RESPIRATORY FAILURE

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FOR the past decade or so clinicians have been approaching the problems of cardiac and renal failure along physiological lines, thinking in terms of cardiac output, glomerular filtration-rates, and so on. But they still seem curiously reluctant to use physiological lines of thought in the analysis and treatment of respiratory disease. We now have many comparatively simple and reasonably accurate methods of measuring respiratory function, and these greatly sharpen clinical diagnosis. Yet many British teachers of medicine either ignore them altogether or refer to them as some sort of activity of backroom playboys and not the sort of thing for a good practical doctor. The current clinical approach is still dominated by "stony dullness" and "dry sounds". The position is much better in the United States, where in a large number of centres adequate physiological investigation of respiratory disease is regarded as normal procedure. The writers of the respiratory sections of American textbooks base their presentation at least as much on the physiological approach as on the purely morbid-anatomical.

Perhaps all this is due to the innate conservatism of the Old World; but the fault is not solely that of the clinician. It is also that of the physiologist, because in some British medical schools the treatment of respiratory function is still frozen at the stage of "lung statics".

Clinically the concept of respiratory failure, while it has long been obvious in such gross asphyxial conditions as laryngeal obstruction, has had comparatively little attention in the many other conditions which involve the lungs. Perhaps too much emphasis has been placed on the effect of these conditions on cardiac function, and the resulting varied symptoms have been regarded as cardiovascular rather than respiratory in origin.

Respiratory failure can be defined simply as that condition in which the amount of oxygen and carbon dioxide in the blood-stream is altered by an abnormality of the respiratory system. On the analogy of other systems we can recognise a preliminary stage of "respiratory insufficiency" in which blood-gas levels, normal at rest, become abnormal during exercise.

An analysis of the mechanisms of respiratory failure falls naturally into the three zones of respiratory function.

Ventilatory Zone

The ventilatory zone is concerned with the maintenance of the alveolar gas tensions at such a level as will ensure that pulmonary capillary blood is saturated with oxygen before it leaves the respiratory portion of the capillary and that it has rid itself of the necessary amount of carbon dioxide over the tension range 46–40 mm. Hg. This requires, on the purely mechanical side, appropriate function of the bellows mechanism of the chest and a configuration of the airways, in respect of relative diameters, &c., which will ensure a uniform distribution of inspired air. Furthermore the general texture of the lungs must be such that an excessive amount of work is not done in distending them. The rate and depth of respiration are regulated by reflex arcs which sense the blood-oxygen tensions (from chemoreceptors principally in the carotid sinus) and the carbon dioxide and pH of the blood passing through the respiratory centre in the medulla. Proprioceptive impulses from the lungs and chest wall also play a part in regulating depth and rate of respiration.

A variety of physiological measurements are appropriate to the ventilatory zone. Of these the most useful give some index of the amount of air that can be moved per unit of time.

One of the simplest is the Wright peak expiratory flowmeter (P.F.M.) † known more familiarly as the "huffer". This is an adaptation of the anemometer used in a meteorological station to indicate the velocity of wind. The patient is merely asked to blow out as hard and as fast as he can through this instrument and a needle jumps up to the maximum velocity attained, which in normal adults is of the order of 500 litres per minute (Wright and McKerrow 1959).

There are many other ways of measuring the maximum breathing capacity (M.B.C.), such as by having the patient breathe as hard as he can into a bag of the Douglas type with the mouthpiece arranged so that inspiration is from the external air. The precise time of 12–15 such breaths is recorded. The volume is then measured in litres, converted to the equivalent volume at 37°C and 760 mm. Hg, and expressed as the volume per minute. In normal adults it is of the order of 150 litres.

A lot of useful information about ventilation can be obtained from a simple spirographic tracing, provided the drum can go fast enough to adequately display a single breath. If the spirometer is of the type described by Bernstein et al. (1952) it can be used for recording the maximum breathing capacity. For this purpose the ordinary Benedict-Roth spirometer, which has been a feature of the clinical physiological laboratory for the past thirty years, is quite unsuitable because of the inertia of its moving parts and because its resonance frequency is about 0·5–1 cycle per second, which means that it overswings grossly when the subject breathes rapidly. The expiratory flow-rate can be measured from the straight part of the downstroke of a spirogram of a forced expiration, provided the drum speed is fast enough to open up the time base.

There is still a place—though not a very large one—for the measurement of the divisions of lung volume, such as vital capacity, inspiratory capacity, and expiratory reserve volume, and also for the measurement of functional residual capacity by the closed-circuit helium-dilution method (McMichael 1939) or the open-circuit nitrogen method (Darling, Cournand, and Richards 1944). From these data the total lung capacity can be calculated. These measurements, although often distorted in disease, do not provide very specific help, because the changes are common to a wide variety of disorders.

An important aspect of ventilation is the efficiency with which each inspiration is mixed with the pre-existing air in the lungs.

Of the various ways of measuring this perhaps the cheapest is to arrange that the patient breathes pure oxygen for seven minutes, by which time a normal person should have reduced the nitrogen content of his expired air to less than 2·5% (Cournand et al. 1941). Values of 15–20% are common in seriously impaired distribution.

* The Frederick Price lecture given to the School of Physic, Trinity College, Dublin, on Nov. 24, 1959.

† Made by Airmed Ltd., 16, Wigmore Street, London, W.1.

Undoubtedly the most convenient method at present available is the single-oxygen-breath procedure, in which, with the aid of a nitrogen meter, a record is made of the nitrogen content of the expiration immediately after a maximal inspiration of oxygen (Comroe and Fowler 1951). In the normal person, as soon as the dead-space gas consisting of pure oxygen is expired, the nitrogen content rapidly climbs to a plateau which is very nearly flat: at any rate its slope is no more than equivalent to 1·5% of nitrogen increase from the 750 ml. to the 1250 ml. levels of expiration. Defective distribution of air is indicated by replacement of the plateau by a gentle ascent terminating with gas which has so much nitrogen in it as to show that comparatively little of the maximum breath of oxygen has penetrated to that part of the lung.

Diffusion Zone

Oxygen and carbon dioxide have to cross the thin layer of fluid and endothelium which separates alveolar gas and capillary blood. Normally this is only about 2 μ thick. The rate at which gas traverses this pathway is governed by the difference in tension at the two extremities, the length of the pathway, and the specific solubility and diffusibility of the gas concerned. In this respect normal gaseous exchange requires the absorption of oxygen and the elimination of carbon dioxide at a resting volumetric equivalence sufficient to satisfy metabolic demands and to maintain a ratio between the two gases of approximately 5 : 4. This latter value is set by the overall respiratory quotient of the individual.

Since carbon dioxide is much more diffusible (20 : 1) than oxygen, the normal tension difference of only 6 mm. (46–40) between the carbon-dioxide tension of mixed venous blood and that of alveolar air is sufficient to ensure the elimination of an adequate amount. In fact the carbon-dioxide tension of the alveolar air and of the arterial blood leaving the lungs is identical. This is not true of oxygen, which is so much less diffusible that even at the comparatively high tension difference between 104 mm. Hg in the alveoli and 40 mm. Hg in mixed venous blood, hæmoglobin is barely saturated by the time it leaves the capillary. Even in health, there is a small tension difference (9 mm.) between the alveolar air and arterialised blood, although this is partly due to shunting.

Estimation of the efficiency of diffusion is essentially by the study of blood-gas levels and their relation to alveolar tensions.

The important measurement (Riley et al. 1951) is the amount of oxygen passing across the membrane per millimetre difference of oxygen tension (diffusion capacity). Technically this is not a very easy measurement because it requires an arterial puncture so that the carbon-dioxide tension of the arterial blood can be measured. This is regarded as identical with the carbon-dioxide tension of the alveolar air—from which, and from the exchange ratio, we can calculate the oxygen tension of the alveolar air. The oxygen tension of the arterial blood is also measured, thus enabling the gradient between alveolus and capillary to be obtained.

This is not, however, quite so straightforward as it looks; for part of the difference between alveolar and arterial oxygen tensions is due to the admixture of a certain amount of blood which has bypassed the alveoli or—what comes to the same thing—has passed through imperfectly ventilated alveoli. Fortunately Riley et al. (1951) with great ingenuity discovered that this admixture factor could be rendered negligible by making the measurements during inhalation of only 14% oxygen. It is thus possible to measure the alveolar-capillary gradient due to membrane factor—i.e., membrane thickness.

There is, however, one desirable measurement which cannot yet be made directly in man and that is the area of the membrane. A reduction of diffusion capacity by half could theoretically be due to a doubling of the mean thickness of the alveolar-capillary pathway or a halving of the area of the alveolar-capillary interface. Fortunately, in practice, this is not usually a serious difficulty, because collateral evidence often indicates which of those two parameters is at fault. For instance, when the patient has a collapsed lung or has had lung tissue removed, a reduction in diffusing capacity is obviously due to loss of area.

There are other methods of measuring diffusing capacity—notably the carbon-monoxide-single-breath method, which, in outline, consists in measuring the amount of carbon monoxide absorbed from a single breath held for ten seconds (Krogh 1914–15, Bates and Christie 1950). The affinity of hæmoglobin for carbon monoxide is so high that for all practical purposes the carbon-monoxide tension of pulmonary capillary blood can be taken as zero. Therefore the gradient is simply the mean carbon-monoxide tension of the alveolar air. This method, however, does not provide for estimation of the admixture factor.

The foregoing diffusion tests are admittedly beyond the scope of any but a specialist laboratory. Fortunately a lot of useful clinical information can be obtained from the measurements of the blood tensions of oxygen and carbon dioxide.

The normal person has an arterial-blood oxygen saturation of 95%, the difference between that and 100% being due chiefly to the normal amount of alveolar shunting. Abnormal oxygen unsaturation of arterial blood, if severe enough, will lead to visible cyanosis, although it must be remembered that the shape of the curve relating the oxygen content of hæmoglobin to the oxygen tension is such that when cyanosis is actually visible the oxygen tension of arterial blood has dropped 40 or 50 mm. Hg. It is wise, if the patient is fit enough, to have him do some mild exercise while the arterial needle is in position; for in many conditions, whereas oxygen saturation is normal at rest, it falls markedly on exercise. Now, in the absence of gross shunting, arterial unsaturation is due to one of two factors—either a ventilatory defect lowering alveolar oxygen tension (as in ventilatory insufficiency) or severe loss of diffusion capacity (as in alveolar-capillary block). If, however, at the same time the carbon-dioxide tension of the arterial blood be measured, then these two causes of unsaturation can be sharply differentiated. If poor alveolar ventilation be the cause, then, just as the oxygen tension of alveolar air is too low, so will the carbon-dioxide tension be too high—because, as it must be eliminated, it will accumulate in the plasma until it attains the 6 mm. ascendance over alveolar carbon-dioxide tension necessary for escape. Therefore, anoxia plus hypercarbia means ventilatory insufficiency. On the other hand, in alveolar-capillary block, carbon dioxide, owing to its high diffusibility, still diffuses out at normal tensions. Indeed, the hyperventilation may actually wash carbon dioxide out of the blood-stream, leading to an abnormally low arterial tension.

The differentiation between those two important types of respiratory defect has been simplified even further by the direct measurement of the alveolar carbon-dioxide tension. As Plesch (1909) originally pointed out, and as Collier (1956) and Campbell and Howell (1958) have emphasised, the carbon-dioxide content of expired alveolar air is identical with that of mixed venous blood when the subject has rebreathed to equilibrium with a bag of air. The addition of 6 mm. to this value can be taken as a good indication of the carbon-dioxide tension of arterial blood. A method very useful in routine clinical practice is to have the patient breathe in and out of a bag

containing pure oxygen. After a minute and a half this bag has a carbon-dioxide content very close to that of the patient's alveolar gas. The bag is then laid aside for a few minutes and the patient then breathes in and out of it for twenty seconds, by which time the carbon-dioxide content of the bag is identical with that of the alveolar gas and of the mixed venous blood.

Estimation of the carbon-dioxide content can be done rapidly with an infra-red analyser or somewhat less rapidly by the Haldane method or any of its modifications. This procedure promises to be of great value in routine clinical work, because it will show an element of hypercarbia in many acute states in which it has not been suspected (Griggs et al. 1958).

Perfusion Zone

The study of this zone consists essentially in measurements of flow and pressure in the pulmonary circulation. Cardiac catheterisation now enables pressures to be measured at all points from the great veins up to the " wedge " point, when the pressure closely approximates to that in the pulmonary veins and in the left auricle. Flow for periods of several minutes is measured by dividing the arteriovenous difference across the lung into the amount of oxygen taken up (Fick principle) or by the use of tracer substances such as Evans blue, Coomassie blue, or radioactive substances such as ^{24}sodium or ^{131}iodinated albumin.

As regards pulmonary pressures, hypertension is the usual defect. It is due to physical reduction of the vascular bed (as in emphysema), or obstruction of the vessels (as in multiple pulmonary embolisation), or low oxygen tensions (as in long-continued hypoventilation) (Cournand 1950). In many slowly progressive pulmonary disorders the hypertension may not be apparent at rest but is obvious during exercise. The normal pulmonary vascular bed can accommodate a several-fold increase in flow with only a slight elevation of the pressure. However, when vessel walls are diseased or the oxygen tension of the inspired air is low, the same increase in flow causes very pronounced hypertension. This illustrates the great value of " testing under load ", which is in many respects of much greater importance than merely ascertaining resting values (Riley et al. 1948).

Ventilation-perfusion ratio

A consideration of the combined influence of ventilation and perfusion leads to the important concept of the ventilation-perfusion ratio (Riley and Cournand 1949). It has always been clear that the proportion of carbon dioxide eliminated to oxygen absorbed—i.e., the respiratory quotient—for the whole body is determined by the metabolic behaviour. On an average mixed diet this ratio is 0·8.

Thus the proportion of ventilation to perfusion in the lungs must be set so as to effect this exchange. This does not, of course, mean that each alveolus must have precisely the same exchange ratio; but the mean level of all alveoli must conform. If the whole lung, a lobe of a lung, or a single alveolus is hyperventilated, then an abnormally great quantity of carbon dioxide is eliminated but very little extra oxygen can be taken up: that is to say, the exchange ratio is greater than unity. On the other hand if ventilation be subnormal, or—what comes to the same thing—perfusion is disporportionately great, then the elimination of carbon dioxide will be reduced more than the absorption of oxygen. This situation is seen in its most extreme form when an airway is completely blocked and the gas exchange is so slight that the bubble comes virtually into gaseous equilibrium with mixed venous blood.

It is clear that in many disease conditions this delicate proportion between ventilation and perfusion is disturbed in varying degrees ranging from scattered alveolar dysfunction through a lobe or single lung up to disturbance of the whole respiratory system.

Lung Mechanics

An important development in the physiology of respiration was an analysis of the mechanics of ventilation by a study of the simultaneous pressure-volume values during a single respiratory cycle (Rohrer 1915). This method is the basis of a mathematical consideration of the function of reciprocating steam engines, internal-combustion engines, and pumps.

A force which has to be overcome in ventilation is resistance to stretch of the lungs and chest wall, which during normal respiration behave as an elastic structure in the middle or rectilinear part of its expansion/contraction range. This resistance obviously increases with increasing depth of respiration, and if it were the only opposition to respiration a plot on x and y axes of the simultaneous values of pressure and volume of a respiration would yield a straight line the angle of which would be a measure of the resistance of the lung and chest wall to stretch.

Other non-elastic forces are developed in moving air through the air-passages and in moving tissue planes over each other. These increase with the speed of breathing and disappear altogether for a brief period at the height and depth of respiration. The effect of this non-elastic resistance is to deviate the pressure/volume trace from a rectilinear form. In fact, its normal form is that of an ellipse, the area of which is proportional to the work done in overcoming non-elastic resistance whereas the area of the right-angle triangle of which the long axis of the ellipse forms the hypotenuse is proportional to the work done in overcoming elastic resistance. This type of analysis is proving a useful diagnostic tool, because it differentiates sharply between respiratory disability due principally to airway obstruction and disability due principally to diffuse stiffening of the lungs. With airway obstruction the area of the loop is much increased; indeed, it may become roughly circular. With stiffening of the lungs, on the other hand, the chief alteration is in the slope of the long axis in the direction which indicates a reduction in change of volume per unit of pressure change—i.e., a reduction in what is known technically as the " compliance " (Fenn 1951, Christie 1953).

The measurements for this sort of study are first of all the volume displacement during a breath, which is readily measured with a flowmeter connected to a mouthpiece or by a special lightweight spirometer (Arnott, Butler, and Pincock 1954). Intrathoracic volumes are obtained from a balloon placed in the œsophagus. Volume displacements and intraœsophageal pressures give the mechanical behaviour of the lungs alone; but if the subject is enclosed in a Drinker-type respirator and is breathed passively, the pressure changes in the casket compared with the volume displacements give a mechanical picture of the thoracic cage along with the lungs. The difference between these two sets of measurements yields a value for the work done, both elastic and non-elastic, in moving the chest walls alone.

Causes of Respiratory Failure

Just as the functional assessment of the respiratory system falls naturally into certain zones, so the diseases impairing respiration can be grouped correspondingly.

Ventilatory impairment is due to any process which interferes with the normal function of the bellows mechanism, either in its moving parts or in its control mechanism. Probably the commonest causes are those which lead to airway obstruction, such as bronchitis,

emphysema, asthma, and tracheal compression. There are processes which interfere with the action of the thoracic cage or pleura—e.g., kyphoscoliosis, ankylosing spondylitis, gross obesity, injury to the chest wall (either accidental or operative), scleroderma, pleural effusion, thickened pleura, and pneumoconiosis. Neurogenic control may be impaired by an intracranial disease (vascular, neoplastic, or traumatic), barbiturate poisoning, paralytic poliomyelitis, polyneuritis, myasthenia gravis, progressive muscular atrophy, porphyria, or muscle-relaxant drugs of the curariform type.

Ventilatory function may also be upset temporarily by a psychological crisis such as hysterical overbreathing.

Diffusion defects may arise from any condition which interposes on an extensive scale any new material—be it fluid, cellular tissue, or connective tissue—between alveolar air and capillary blood. Among such conditions are pulmonary œdema, which leads to both free fluid in the alveoli and fluid separating the alveolar and capillary walls (e.g., in chronic left-sided cardiac failure and particularly mitral-valve disease) and also disorders which are associated with a diffuse overgrowth of tissue (e.g., sarcoidosis, pneumoconiosis, berylliosis, scleroderma, radiation fibrosis, pulmonary histiocytosis, lymphangitic carcinomatosis, and the peculiar diffuse inflammatory process called the Hamman-Rich syndrome) (Arnott 1959).

Pressure defects arise in any process which impairs the flow of blood through respiratory capillaries. In its most extreme form it may be the result of the lodgment of an embolus in the main pulmonary artery—a process which so much interferes with circulation as to cause rapid death. On the other hand blockage of a right or left pulmonary artery, by an embolus or surgical treatment, results in surprisingly little functional impairment. The vascular bed of the remaining lung, provided it is reasonably healthy, can dilate sufficiently to accommodate the entire blood-flow without any great elevation of pressure. When a lung is removed, functional impairment is comparatively slight; but when blood-flow to the lung is greatly reduced though ventilation remains normal, a serious ventilatory defect results which takes the form of a greatly increased dead-space effect. Localised vascular disease, such as may be caused by tuberculosis, bronchiectasis, injury, or neoplasm, is not as a rule of serious functional moment, because any disturbance of ventilation/perfusion ratio can be compensated by the normal areas. Diffuse vascular disease is an important cause of pulmonary hypertension, and may be due to such processes as multiple embolisation from thrombophlebitis and chorionepithelioma (Bagshawe and Brooks 1959) or may be the reflection of cardiac disease such as mitral stenosis and left-to-right shunting.

Pathological Mechanisms

Apart from extrathoracic disease interfering with the central control of respiration, the principal structural effects of disease can be regarded as:

(*a*) Airway obstruction.

(*b*) Stiffening of lungs with increase of the diffusion pathway.

(*c*) Reduction of pulmonary vascular bed.

The principal functional effects of respiratory disease are:

(*a*) Arterial unsaturation with consequent cyanosis and a varying degree of polycythæmia.

(*b*) Where alveolar ventilation is subnormal, carbon-dioxide retention occurs, which in time leads to a diminished sensitivity of the respiratory centre to carbon-dioxide and progressive hypercapnia.

(*c*) Retention by the body of base (mainly sodium bicarbonate), in order to buffer the retained carbon dioxide, aggravates the pulmonary hypertension and the œdema.

(*d*) Pulmonary hypertension with consequent right ventricular hypertrophy and ultimately failure with systemic venous hypertension and œdema.

In the early stages of respiratory disease these functional effects become apparent only during exercise. For instance, until emphysema is advanced, the arterial oxygen saturation is normal at rest though it may drop considerably during exercise. Similarly the pulmonary arterial pressure may be normal at rest for a time but rises quite abnormally during exercise.

Clinical Picture of Ventilatory Failure

The common cause of this syndrome is airway obstruction resulting from inflammatory reaction of the lining mucosa. This is a common consequence of infection (as in bronchitis following coryza or influenza), an allergic stimulus (as in asthma), or chemical damage (as in the inhalation of tobacco smoke or industrial pollution). With this air-passage inflammation there is often emphysema, which, whatever its origin, is certainly associated with faulty air distribution, alveolar hypoventilation, much distortion of the ventilation/perfusion ratio, a reduced pulmonary vascular bed, and pulmonary hypertension.

In recurrent bronchitis—the commonest cause of ventilatory disability—patients tend to show a steady level of respiratory disability with periodic crises of acute respiratory failure due to respiratory infection, allergic attacks, or severe atmospheric pollution.

Respiratory failure is marked by dyspnœa: the effort of breathing increases because the airway is obstructed by swollen mucosa and, above all, retained secretions. If emphysema is severe the position of the thoracic cage is mechanically embarrassing. Additional factors causing dyspnœa are carbon-dioxide retention, to which the respiratory centre is only partially acclimatised, and hypoxia which stimulates the carotid-sinus and aortic chemoreceptors. In all severe cases there is cyanosis due to arterial desaturation: if not obvious at rest, it is plain after exercise such as a bout of coughing. The most obvious effects of carbon-dioxide retention are principally in the nervous system. Here one must admit that there is not yet any clear separation between the neural effects of hypercarbia and anoxia; but at any rate both processes are present in respiratory failure of ventilatory origin, and are responsible for mental confusion which in the past has been regarded uncritically as toxic or febrile delirium. The patient is forgetful, and a few questions—" what day of the week is it? ", " what did you have for breakfast? ", " which party won the election? "—may at once uncover a gross abnormality. Such patients tend to be drowsy and the relatives may complain that they fall asleep in the middle of a conversation. Coarse irregular muscle twitching is usually present and can be clearly seen when the patient stretches out his arms with the wrists dorsiflexed. The twitching resembles the " liver flap " of hepatic failure.

The hypercapnia may be associated with an exacerbation of congestive cardiac failure, shown by distended neck veins and gross œdema. The extremities are warm, the pulse is full, and the blood-pressure slightly raised (Westlake, Simpson, and Kaye 1955). The differential diagnosis of such a state of respiratory failure is greatly helped by the background of the patient. Except during epidemics of virulent influenza, the syndrome rarely develops suddenly in a person who has not been obviously

ill. The patients are usually known bronchitics and their acute attack is precipitated by an infection of the upper respiratory tract, the whole syndrome arising commonly in winter about a week after the commencement of an attack of the prevailing epidemic. The circumstances of the event should prevent any confusion with attacks of pulmonary œdema due to hypertensive cardiac failure, myocardial ischæmia, or mitral stenosis. The respiratory failure can be conclusively demonstrated by finding oxygen unsaturation and raised carbon dioxide in a sample of arterial blood. Even more simply the determination of the alveolar carbon dioxide by the Campbell-Howell method will confirm the diagnosis.

At hospitals making systematic tests of arterial blood gases or alveolar carbon dioxide respiratory failure is found, often unexpectedly, in a substantial proportion of middle-aged or elderly people with congestive cardiac failure who have been regarded as victims of coronary vascular disease and whose underlying respiratory condition has been inadequately assessed. The effect of giving such patients pure oxygen may confirm the diagnosis (Donald 1949). The elevation of the oxygen tension of the inspired air rapidly offsets the alveolar hypoventilation in respect of oxygen; cyanosis is abolished and the patient is soon pink and placid—far too placid in fact, for he may sink into coma with aggravation of the muscle twitching. The rate of respiration decreases and its amplitude is less. Owing to the insensitivity of the respiratory centre to carbon dioxide, the respiratory drive of such patients depends unduly on the hypoxic stimulus. Once this is corrected, ventilation becomes less and carbon-dioxide retention increases—perhaps dangerously.

In patients in whom the respiratory element has not been recognised and who have been treated along conventional lines for cardiac failure, the response to digitalis and diuretics is often very slow; but when the ventilatory insufficiency is corrected the pulmonary pressure falls, venous congestion subsides, and œdema disappears.

Treatment of Respiratory Failure of Ventilatory Origin

When a patient presents the sort of picture I have described, the aim of treatment is to improve alveolar ventilation. Antibiotics are necessary for the infection, which is usually important. In a severe case full doses of penicillin and tetracycline are useful. The removal of secretions can be assisted by a steam tent, which, old-fashioned though it may be, is an excellent means of keeping mucus fluid. Aerosols may help, and if there is any bronchospasmic element isopropyl-noradrenaline should be included in the aerosol. Oxygen should be given, preferably in a tent because such patients do not readily retain a mask or nasal catheter. A close watch should be kept for any increasing stupor or convulsions. To prevent these, the period of oxygen breathing may be only forty minutes in the hour, followed by twenty minutes breathing room air; but marked hypercarbia is an indication for more ventilation *not* for less oxygen. In ventilatory failure the use of 5% carbon dioxide in oxygen is, of course, completely wrong.

Ventilation can be stimulated chemically by the use of aminophylline (2·5% solution) and nikethamide (25% solution) given in an intravenous drip under the close personal supervision of the physician. Large doses are usually necessary, and the amount required is that which produces the required increase in ventilation without (in the case of aminophylline) nausea and vomiting or (in the case of nikethamide) troublesome convulsions. Hence the need for a physician to keep his hand continually on the drip-cock (Hugh-Jones 1958).

Sometimes all these measures fail, because of the amount and stickiness of the secretions or because one cannot correct cyanosis without depressing ventilation dangerously. The treatment then is tracheotomy so that bronchial secretions can be sucked out and a positive-negative pressure respirator (e.g., of Smith-Clark type) can be connected to the tracheal opening. This may save a moribund patient (Davidson 1959). Once the whole ventilatory mechanism is under artificial control, the risk of hypercarbia has gone: the blood carbon-dioxide tension is likely to revert to normal within an hour or two and the general electrolyte balance should be normal within two or three days. The risks of respiratory depressant drugs—particularly morphine preparations—are obvious, although once tracheotomy with artificial respiration is established their depression of the respiratory centre is no longer of consequence.

When the role of respiratory failure was first recognised and these active therapeutic measures were introduced it was thought that the improvement might only be transient and would rarely enable the patient to regain anything approaching a useful life. But the extent of recovery may be very great; indeed, many patients rescued from an acute attack of respiratory failure have remained in good health indefinitely.

Application of the principles I have outlined would considerably improve the outlook in cases of chronic ventilatory defect. With differences appropriate to the causal disease, this picture of ventilatory failure is reproduced in many disorders—all of them having the capacity to cause alveolar underventilation.

Some less familiar causes of respiratory insufficiency and failure have been recognised recently.

The grossly obese, with weights above 20 st., often have quite severe respiratory inadequacy (Hackney et al. 1959). Not only are they dyspnœic on slight exertion but they are often mentally sluggish and drowsy. This has been shown to be due to carbon-dioxide retention. The defect here is the great weight of the thoracic integument and the high intra-abdominal pressure caused by the massive deposits of fat. The expiratory reserve volume is much reduced and the ratio of dead-space air is increased. All this leads to defective alveolar ventilation, habituation of the respiratory centre to high pCO_2, and chronic anoxia. Polycythæmia, pulmonary hypertension, and ultimately congestive cardiac failure supervene.

Gross thoracic deformity of the kyphoscoliotic type has long been known to terminate sometimes in congestive cardiac failure. Recent studies have shown that this is cardiorespiratory failure, the result of alveolar hypoventilation and cor pulmonale. It is due to an unusual pattern of breathing which, while it minimises the work and energy required to move the deformed chest, is nevertheless insufficient to secure adequate alveolar ventilation. An additional factor in these people is that the pulmonary vascular bed is smaller than normal (Bergofsky et al. 1959).

Alveolar-capillary Block Syndromes

As already explained, any process which increases the diffusion pathway so much that it seriously impairs oxygen saturation of hæmoglobin will produce the alveolar-capillary block syndrome. Many of the usual causes have been enumerated (Arnott 1959, 1960). The clinical picture varies to some extent according to the causal process; but, provided this is comparatively gradual in its onset (as

in sarcoidosis), the first disturbance is dyspnœa. This is not the laboured obstructed breathing found in chronic bronchitis or asthma; for the greater ventilatory volume is secured mainly by an increase in the rate rather than the depth of respiration. At first this increase is noticeable only on exercise; but, once the disorder is established, the resting respiratory rate is at least 20 per minute, and in the later stages it may be continually as high as 35–40 with little slowing during sleep. While still approaching the bedside I have been able to make the diagnosis from the chart, which showed the respiratory rate to have been around 30, with little or no fever, for many days. Orthopnœa is absent except when pulmonary hypertension has led to right heart-failure.

The cause of this accelerated respiration is probably the generalised stiffening of the lungs, which means that depth of respiration is attainable only by an inordinate expenditure of work. From the ventilatory angle the rapid, rather shallow, breathing is inefficient in that it exaggerates the dead-space effect, which reduces alveolar ventilation. For a time at least, an increased diffusion pathway can be compensated by an elevation of alveolar oxygen tension, through better ventilation. Normally the oxygen tension of room air is about 150 mm. whereas that of alveolar air is about 104.

The diffuse stiffening of the lungs has led to the clinical phenomenon which has come to be known as the " door stop " sign. This is observed when the patient is asked to take a deep inspiration and the effort is arrested abruptly.

I well remember a patient with a diffuse alveolar-capillary disorder in whom bronchoscopy was carried out under general anæsthesia. Having inserted a tracheal tube and given a muscle-relaxant drug, the anæsthetist settled down to ventilate the patient by rhythmic contraction of the bag. He soon discovered that his compression of the bag was opposed firmly by the indistensibility of the patient's lungs. The extensive thickening of alveolar walls which was demonstrated at necropsy some weeks later amply explained this defect.

Tachycardia is quite often present. From an early stage there is usually some arterial unsaturation, but only when the disease is well established is this sufficient to cause cyanosis, and only in the late stages is the cyanosis evident during rest: it can be abolished by raising the oxygen tension of the inspired air. Clubbing of the digits is variable in occurrence and is associated with an abnormally large blood-flow in the terminal phalanges, the precise cause of which is unknown. Most patients with alveolar-capillary block have a cough, but sputum is usually scanty and non-purulent. They usually experience extreme fatigability from an early stage, and by the time arterial unsaturation is substantially at rest they lose weight. The general upset depends on pure anoxia without the carbon-dioxide poisoning seen in ventilatory obstruction. In this respect the picture approximates to mountain sickness. Although oxygen-lack by itself causes headache, anorexia, and some mild confusion with hallucinations, the mental state is usually comparatively clear until near the end—in contrast to cases with ventilatory defects, in which carbon-dioxide retention causes stupor and twitching.

Polycythæmia is seldom present—probably because the whole course of alveolar-capillary block is rarely long enough to allow of this adaptation.

Clinical examination of the chest usually shows little abnormality other than some moist accompaniments. Prolonged expiration and dry sounds of bronchial obstruction are absent. As many of the causes of alveolar-capillary block involve the pulmonary vascular bed, pulmonary hypertension with its liability to congestive cardiac failure is often present.

The extent and character of radiological changes depend very much on the cause of the syndrome. It is important to realise that a patient with a severe degree of block may show virtually no radiological changes, or a diffuse fine mottling. Obliteration of costophrenic angles and prominence of fissure lines may be visible.

The principal physiological changes are the increased alveolar-capillary gradient with arterial unsaturation and a normal or reduced arterial carbon-dioxide content. The alveolar carbon dioxide is also normal or reduced. This arterial unsaturation can be fully corrected by inhaling oxygen.

A spirogram shows no evidence of obstruction. The total capacity and total lung capacity are reduced, almost entirely through curtailment of the inspiratory capacity.

Pressure/volume curves of the respiratory cycle show a reduced compliance, as the result of the stiffening of the lungs, with a normal non-elastic component indicating free airways.

As the airways are not involved, pulmonary mixing is normal and tests of maximum breathing capacity (such as the peak expiratory flow-rate) give values either low normal or very slightly impaired. These values are much better than they would be if the syndrome were due to ventilatory defect.

Although the diagnosis of alveolar-capillary block, to be precise, requires considerable cardiorespiratory laboratory resources, a reasonable diagnosis can be made on the basis of dyspnœa, hyperventilation, and tachypnœa, in the presence of diffuse finely dispersed radiological pulmonary lesions and the absence of bronchial obstruction or emphysema. The diagnosis will be strengthened if there is post-exercise cyanosis which can be completely abolished by breathing oxygen.

There is, of course, a wide range of possibilities as to the disease which may be causing the defect. One which I have already mentioned is the curious disorder which has come to be known as the Hamman-Rich syndrome (Rubin and Lubliner 1957). This begins usually as a respiratory-tract infection of the inflammatory type but goes on to develop the clinical picture of alveolar-capillary block leading to death within a few months. The alveolar septa are found to be diffusely thickened with young connective tissue, and the alveolar endothelium instead of being extremely thin becomes cuboidal or even columnar.

Treatment of the alveolar-capillary block syndrome must be directed at the causal process. For instance, the treatment of sarcoidosis with corticoids is often successful; and radiation reaction, provided no further radiotherapy is given, sometimes subsides satisfactorily. Unfortunately, many of the causes are irreversible end-stages of disease. Anoxia is treated by oxygen inhalation, but where the disease is progressive the patient will become increasingly dependent on his oxygen lifeline. There is no physiological objection to oxygen therapy; for, in contrast to cases of ventilatory insufficiency, carbon-dioxide retention is absent. Any concurrent factor which causes bronchial obstruction, such as inflammation or hypersensitivity, should be treated appropriately.

Conclusion

I hope I have made it clear that order and disorder in pulmonary function (Arnott 1955) can be interpreted on the basis of physical chemistry and that much that was

previously obscure thus becomes logical and leads naturally to rational treatment.

We have to recognise the importance of respiratory insufficiency in such common conditions as bronchitis, bronchopneumonia, chest-wall injuries, and barbiturate poisoning. Informed and intelligent treatment of such disorders will save lives.

It is a great pleasure to acknowledge the debt I owe to my colleagues who have tried so hard to guide me in this field, in particular Prof. Kenneth Donald, Prof. Owen Wade, Prof. A. L. d'Abreu, Dr. George Whitfield, Dr. John Bishop, Dr. Peter Harris, and Dr. John Butler.

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AUTOIMMUNE HÆMOLYTIC ANÆMIA WITH ACUTE RENAL FAILURE DUE TO PHENACETIN AND *p*-AMINOSALICYLIC ACID

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CERTAIN drugs, such as acetylphenylhydrazine, when given to normal subjects in sufficiently high dosage, cause hæmolysis. A different kind of drug-induced hæmolysis depends on hypersensitivity to a particular drug or drugs. Two mechanisms for this have been described:

1. The drug may be adsorbed to the red blood-cells; and, with the drug-erythrocyte complex as antigen, "autoantibodies" are formed which subsequently destroy the patient's erythrocytes in the presence of the drug.

2. The erythrocytes, because of an inherent enzyme defect, are sensitive to the hæmolytic action of drugs in doses which are not normally harmful (Beutler et al. 1954, 1955, Carson et al. 1956).

Harris (1956) was the first to give a complete report of an example of the first mechanism: he described a case of sensitivity to the antimony-containing drug, stibophen. A similar mechanism has been described in hæmolysis due to such drugs as quinidine (Freedman et al. 1956), methoin (Snapper et al. 1953), and quinine and phenacetin (Muirhead et al. 1958).

The second mechanism is now known to be responsible for the hæmolytic episodes which sometimes follow treatment with primaquine (Dern et al. 1954), nitrofurantoin (Kimbro et al. 1957), sulphonamides and *p*-aminosalicylic acid (P.A.S.) (Szeinberg et al. 1957), and vitamin-K substitutes (Zinkham and Childs 1957) and in favism (Szeinberg et al. 1957).

We report here the production of hæmolysis and acute renal failure in two patients, of whom one was sensitive to phenacetin and the other to P.A.S. In each case the presence of an "autoantibody" was demonstrated.

Phenacetin Sensitivity

Phenacetin was introduced in 1887 as an antipyretic and analgesic agent. Despite its widespread clinical use, there are few records of side-effects.

Smith (1958) noted that skin eruptions, cyanosis due to the production of sulphhæmoglobin and methæmoglobin, and anæmia were the commonest toxic manifestations. In addition he referred to renal damage, indicated by hæmaturia, casts, and occasionally oliguria with azotæmia, but detailed case-reports were not given. Wuhrmann and Jasiński (1955) described 35 cases of toxic hæmolytic anæmia after phenacetin ingestion. Females were predominantly affected and an association with pre-existing iron-deficiency anæmia was stressed. The possibility of a sex-linked abnormality of the red-cell-enzyme system was suggested. Marti (1958) recorded anæmia, probably due to hæmolysis, in half of 70 cases of chronic phenacetin overdosage. Meischer and Pletscher (1958) found that the mean red-cell life in patients taking 1–2 g. of phenacetin daily was diminished (but only to levels which a normal bone-marrow could have rectified).

An exact mechanism of hæmolysis due to phenacetin was not described until Muirhead et al. (1958) demonstrated, in a single anæmic patient, a phenacetin-dependent antiglobulin reaction. Phenacetin-induced hæmolysis associated with red-cell enzyme (glucose 6-phosphate dehydrogenase) deficiency has not been reported. Dern et al. (1955) showed, however, that red cells from primaquine-sensitive individuals, when transfused into normal subjects are hæmolysed by other drugs, including phenacetin.

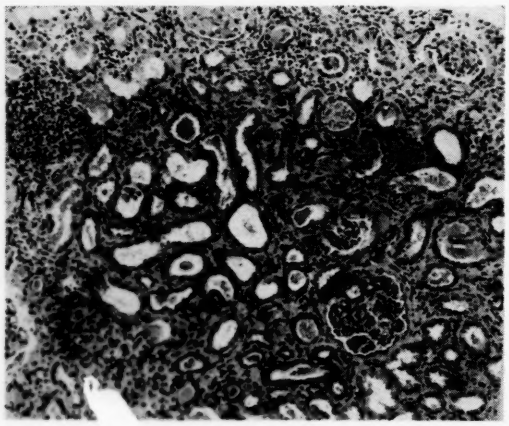
Although the hæmolytic effect of phenacetin has been recognised, acute oliguric renal failure has not been described. The kidneys have, however, been reported to suffer damage after prolonged administration. Spuhler and Zollinfoe (1953) recorded "primary chronic interstitial nephritis" at necropsy in phenacetin poisoning, and raised the question of renal damage in chronic takers of the drug. Lindeneg (1959), too, has correlated chronic renal impairment with long-term phenacetin habituation and suggests that renal papillary necrosis might possibly be caused in this way.

CASE ONE

A 38-year-old white woman was admitted to Dartford Hospital in April, 1958, with jaundice and oliguria of 48 hours' duration. 5 months earlier she had had a similar episode, lasting several weeks, with vomiting, malaise, and jaundice but without obvious disturbance of kidney function. Apart from a history of scarlet fever with nephritis at the age of 7 years, there was no evidence of pre-existing renal disease; in particular she had had no nocturia, dysuria, or œdema.

Examination and Investigations

The patient was anæmic, with icterus of the conjunctivæ. No skin rash was noted, and there was no œdema. The spleen was moderately enlarged and both kidneys were palpable. The liver was not enlarged.



Case 1: renal biopsy specimen taken during diuretic phase of first illness, showing pronounced interstitial cellular infiltration. (× 98.)

Investigation showed a hæmoglobin level of 7·6 g. per 100 ml. and a blood-urea of 233 mg. per 100 ml. In view of this finding and of persistent anuria, the patient was transferred to Hammersmith Hospital for possible treatment by hæmodialysis with an artificial kidney.

Further investigations on admission showed that the hæmoglobin level was unchanged at 7·8 g. per 100 ml., the packed-cell volume (P.C.V.) was 24·5% and the mean corpuscular hæmoglobin concentration (M.C.H.C.) 32%. The leucocyte-count was 4500 per c.mm. and the platelet-count 160,000 per c.mm. The peripheral-blood film showed anisocytosis, with microcytosis, slight polychromasia, and occasional schistocytes. The patient's blood-group was A, rhesus-positive. The total serum-proteins were 7·1 g. per 100 ml., with albumin 3·7 g. per 100 ml. The blood-urea had risen further to 300 mg. per 100 ml.; the serum-potassium was 6·6 mEq. per litre, with a bicarbonate level of 13 mEq. per litre.

Course

Severe oliguria persisted and the patient was treated by a conservative regime for acute liguric renal failure. The blood-urea reached a peak of 450 mg. per 100 ml. on the 10th day of the illness, at which time a satisfactory diuresis took place. Hæmodialysis was not required, and the subsequent course to recovery was uneventful. The hæmoglobin level did not fall further and was restored to normal by transfusion. Examination of the patient's urine in the diuretic phase, and thereafter, showed no abnormality, and percutaneous renal biopsy revealed the appearances of a recovering tubular necrosis with considerable interstitial cellular infiltration (see figure). There was no evidence of glomerular damage.

Anæmia with tubular necrosis of obscure origin was diagnosed, and the patient returned home after 6 weeks to continue convalescence. For the ensuing 5 months she remained well; the hæmoglobin level was maintained, the blood-urea was normal, and there was no proteinuria. On Oct. 27, 1958, however, she suddenly became ill a few hours after the ingestion of 4 analgesic tablets taken for incipient coryza. The patient stated that her lips and hands became blue and she had a cold sensation in her hands and feet. On the following day she vomited profusely, and voided only a small volume of dark urine. She was observed to be jaundiced, oliguria persisted, and she was readmitted to Hammersmith Hospital.

Readmission

On examination the patient was again anæmic and jaundiced. The kidneys and spleen were enlarged to palpation. Investigations showed a hæmoglobin level of 10·4 g. per 100 ml. and 1·4% reticulocytes. The peripheral-blood film showed slight anisocytosis. No sulphæmoglobin or methæmoglobin was detected, but the serum contained methæmalbumin, and electrophoresis showed absence of haptoglobins. (3 days later only a trace of methæmalbumin was present, and the haptoglobins were normal.) Osmotic fragility was normal. The plasma-bilirubin (indirect-reacting type) was 1·2 mg. per 100 ml.; serum-alkaline-phosphatase was normal, and flocculation tests of liver function showed no abnormality.

Severe oliguria persisted for 10 days, the blood-urea rising to 280 mg. per 100 ml. The protein-anabolic steroid norethandrolone (' Nilevar ') was added to the conservative-treatment regime employed during the previous illness, and again hæmodialysis was not required. Following diuresis the patient once more recovered uneventfully, with no evidence of residual renal dysfunction.

Relation of Attacks to Phenacetin

The tablets taken by the patient at the start of the second illness were found to be " A.P.C." and to contain a total dose of 648 mg. of phenacetin. Inquiry established that immediately before her illness in April, 1958, she had taken two ' Veganin ' tablets (each containing 250 mg. of phenacetin); and in October, 1957, when she had suffered obscure malaise with jaundice, she recalled having been given two ' Cojene ' tablets (each containing 300 mg. of phenacetin). Apart from these three occasions, she denied previously taking any form of analgesic.

It therefore appeared possible that phenacetin was responsible for the episodes of anæmia and acute renal failure. An inherent defect in the patient's red-cell enzymes was first sought as a cause for the sensitivity, but the glutathione-stability test (Beutler 1957) was normal. The direct antiglobulin test, on the other hand, was weakly positive. This suggested that the hæmolysis might be due to an autoantibody mechanism.

The patient's serum was then found to contain a factor which, in the presence of phenacetin but not in its absence, was capable of sensitising normal red cells of the patient's blood-group to agglutination by antiglobulin serum. Further hæmatological studies were then undertaken to define the properties of the serum factor more exactly.

The direct antiglobulin reaction was apparently of the non-γ-globulin type—that is to say, the red cells were agglutinated by an antiglobulin serum to which human γ-globulin had been added. However, when the indirect test was carried out using patient's serum, phenacetin, and normal red cells, the non-γ-globulin reaction was shown to be due to the adsorption of complement. When the test was repeated using heat-inactivated patient's serum and phenacetin it was still positive using the normal antiglobulin reagent (no γ-globulin added) but negative with antiglobulin serum to which γ-globulin had previously been added.

The antibody thus appeared to be potentially hæmolytic in vitro, and this was confirmed by the demonstration that the patient's serum, with added phenacetin, brought about the hæmolysis of trypsinised normal red cells and P.N.H. (paroxysmal nocturnal hæmoglobinuria) red cells in the presence of human serum complement. Hæmolysis of normal (untrypsinised) red cells could not be demonstrated. Normal red cells were, however, agglutinated to approximately the same serum dilutions that produced positive antiglobulin tests (table I).

TABLE I—AGGLUTINATION, HÆMOLYSIS, AND SENSITISATION TO ANTIGLOBULIN SERUM BY ANTIBODY PRESENT IN SERUM OF CASE 1

Cells tested	Dilution of patient's serum			Agglutination and lysis
	1 in 1	1 in 4	1 in 16	
Normal	++	±	0	Agglutination (diluent saline)
Normal trypsinised	±	+	0	Lysis (diluent fresh normal serum)
P.N.H.	++	+	0	Lysis (diluent fresh normal serum)
Normal (indirect Coombs test)	+++	+	0	Agglutination (diluent fresh normal serum)

In each test phenacetin was present at a final concentration of 3·3 mg. per 100 ml.
Readings of agglutination and lysis were made after 2 hours at 37°C.
+++, ++, +, ± indicate grades of agglutination and lysis.

TABLE II—SENSITISATION OF NORMAL RED CELLS TO ANTIGLOBULIN SERUM, IN PRESENCE OF VARYING AMOUNTS OF PHENACETIN, BY ANTIBODY PRESENT IN SERUM OF CASE 1

Dilution of patient's serum in fresh normal serum			Final concentration of phenacetin (mg. per 100 ml.)
1 in 1	1 in 4	1 in 16	
+++	++	0	10·0
+++	+±	0	5·0
+++	+	0	2·5
+++	+	0	0·5
+++	±	0	0·05
++	±	0	0·025
±	trace	0	0·005
±	trace	0	0·0025
trace	0	0	0·0005
0	0	0	0·0001

The tests were read after 2 hours at 37°C.
+++, ++, +, ± indicate grades of agglutination.

In all the above experiments control tests using normal serum and phenacetin, patient's serum without phenacetin, and phenacetin alone were set up. No agglutination, hæmolysis, or sensitisation to antiglobulin serum was demonstrated in any of these control tests.

Concentration of Phenacetin and Serum Titre (Table II)

Phenacetin was added to the patient's serum in final concentrations ranging from 10 mg. per 100 ml. to 0·1 μg. per 100 ml. Positive reactions were obtained within the range 10 mg. to 2 μg. per 100 ml. Employing the antiglobulin reaction as a means of detecting sensitisation the maximum titre of antibody demonstrated was 16.

The antibody at first gained in strength with time. Within a few days of the second hæmolytic episode the maximum titre demonstrated, using the agglutination of normal cells, was 2; 3–4 weeks later it was 8; 7 weeks after the onset of hæmolysis it was 16. The titre had fallen to 2 when serum was tested 9 and 24 weeks later.

Reaction with Other Drugs

Drugs chemically unrelated to phenacetin, but known to be capable of causing hæmolysis by a similar mechanism (e.g., quinidine and methoin), did not, in the presence of this patient's serum, sensitise normal red cells to agglutination by antiglobulin serum. Neither did P.A.S., *p*-aminobenzoic acid, sulphadiazine, procaine hydrochloride, and probenecid. On the other hand, the in-vivo metabolic products of phenacetin—paracetamol (' Panadol ') and para-phenetidine—both produced positive reactions. Whereas phenacetin was effective in a final concentration as small as 2 μg. per 100 ml., the necessary minimum concentrations of paracetamol and para-phenetidine were 1·7 mg. and 1 mg. per 100 ml. respectively.

P.A.S. Sensitivity

Since its introduction in 1944, P.A.S. has been widely used in the treatment of tuberculosis, and numerous toxic effects have been reported.

The most serious of these have been liver and kidney lesions (Cuthbert 1950, Livingstone and Street 1950, Mann 1953, Cannemeyer et al. 1955, Hensler et al. 1957) and hæmolysis. Renal damage in the absence of other lesions seems rare, but has been recorded (Owen 1958). Dérot et al. (1956) reported a case of fatal anuria following the intravenous administration of P.A.S. solution. But, although these workers state that there was no clinical evidence of hæmolysis, no hæmatological investigations are recorded. However, on one occasion before her acute reaction to the final P.A.S. infusion, the patient had had lumbar pain, and the terminal oliguria was preceded by the passage of a few millilitres of red urine. Hæmolysis is a well-known but rare complication of P.A.S. therapy. It has been reported most commonly within 24 hours of taking a small oral dose of the sodium salt of P.A.S. in solution, without previous exposure to the drug (Janet et al. 1951, Tondi 1951, Christiaens and Goudemand 1952, Castanier et al. 1954, Claps 1957, Rowland 1958). Phenolic substances have been isolated from the urine in some of these cases (Christiaens and Goudemand 1952, Castanier et al. 1954, Claps 1957). A direct toxic action on the red cells by some degradation product of P.A.S. has been suggested as the most likely explanation of the hæmolysis. Some experimental evidence in support of this was obtained by Castanier et al. (1956). All but one of a group of rabbits given daily doses of discoloured preparations of the sodium salt of P.A.S. died, while all the controls given unaltered P.A.S. survived.

In some cases acute hæmolysis did not begin until after 15 or more days of treatment with the sodium salt of P.A.S. in solution (Sémelaigne et al. 1950) or as tablets (Burkens 1951). In one instance a skin rash was noted at the time of onset of the hæmolysis (case of M. Sémelaigne 1950, more fully reported by Christiaens and Goudemand 1952). The delayed type of hæmolysis may have a different pathogenesis, but may only be related to differences in the preparations of P.A.S. employed. Erythrocyte-enzyme defects have been sought in two cases of hæmolysis due to P.A.S. (Szeinberg et al. 1957, Sansone and Segni 1958) and in one (Szeinberg et al. 1957) a low level of reduced glutathione was found. However, no details are given, either about the type of P.A.S. administered or about blood and urine findings at the time of hæmolysis. No immunological mechanism seems to have been described so far for hæmolysis due to P.A.S.

CASE TWO

A 73-year-old man was found to have pulmonary tuberculosis in 1956 and received treatment with ' Pycamisan ' (containing P.A.S. and isoniazid) irregularly for an uncertain period. In April, 1959, reassessment revealed persistent active infection, and *Mycobacterium tuberculosis* was cultured from the sputum. The hæmoglobin was 12·5 g. per 100 ml. and the blood-urea was 44 mg. per 100 ml.

On April 23, 1959, a second course of chemotherapy was started using streptomycin 1 g. daily, P.A.S. 12 g. daily, and isoniazid 300 mg. daily. The patient's general condition improved over the next few days. Examination of the urine on April 29, 1959, showed minimal proteinuria and a scanty growth of *Staphylococcus aureus* on culture. There was no pyuria, and the blood-urea remained at 45 mg. per 100 ml. No records of urinalysis before the start of chemotherapy are available.

Onset and Course of Hæmolytic Anæmia

On May 7, 1959, after 2 weeks' treatment, the patient became drowsy and anorexic, and the blood-pressure fell to 110/50 mm. Hg. The blood-urea had risen to 124 mg. per 100 ml. although the serum-electrolytes were normal. In consequence the streptomycin was withdrawn. On the following day, the urine was dark brown; it contained more protein than before but no red cells. The hæmoglobin had fallen to 3·9 g. per 100 ml.

Hæmolytic anæmia was diagnosed, and the remaining drugs —P.A.S. and isoniazid—were withdrawn. Prednisolone, 10 mg. t.d.s., was given in an attempt to control the hæmolysis. During the next 48 hours the patient's condition deteriorated rapidly; the blood-pressure fell profoundly and he was treated with noradrenaline and blood-transfusion. Complete anuria, preceded by oliguria of uncertain duration, was now present, and he was transferred to Hammersmith Hospital for possible treatment by hæmodialysis with an artificial kidney.

On arrival, he was semicomatose with deep respirations. There was a generalised fine macular rash suggesting a drug-sensitivity reaction. The blood-urea had risen to 375 mg. per 100 ml., and the serum-bicarbonate level had fallen to 17 mEq. per litre. The serum-potassium was 4·5 mEq. per litre and serum-bilirubin 6·1 mg. per 100 ml. The hæmoglobin was 5·8 g. per 100 ml., and methæmalbumin and free hæmoglobin were present in the serum; haptoglobins were absent. The peripheral-blood film showed evidence of autohæmagglutination, and numerous normoblasts were present. There was marked spherocytosis, anisocytosis, and polychromasia. The

TABLE III—AGGLUTINATION, HÆMOLYSIS, AND SENSITISATION TO ANTI-GLOBULIN SERUM BY ANTIBODY PRESENT IN SERUM OF CASE 2

Cells tested	Dilution of patient's serum				Agglutination and lysis
	1 in 1	1 in 4	1 in 16	1 in 64	
Normal ..	+++	+++	+	0	Agglutination (diluent saline)
Normal trypsinised	++	++	trace	0	Lysis (diluent fresh normal serum)
P.N.H.	+++	+++	+±	trace	Lysis (diluent fresh normal serum)
Normal (indirect Coombs test)	+	++	+	0	Agglutination (diluent fresh normal serum)

In each test P.A.S. was present at a final concentration of 40 mg. per 100 ml.
Readings of agglutination and lysis were made after 2 hours at 37°C.
+++, ++, +, ± indicate grades of agglutination and lysis.

reticulocyte-count was 4%. Osmotic fragility was increased. Bone-marrow aspiration showed erythroid hyperplasia. The patient's blood-group was A, rhesus-positive.

The renal failure was treated conservatively; but attempts to improve the circulatory state prior to hæmodialysis were unsuccessful and the patient died 30 hours after admission. Permission for postmortem examination was not granted.

A diagnosis was made of hæmolytic anæmia and acute oliguric renal failure due to one of the three chemotherapeutic agents employed.

Further Laboratory Investigations

The glutathione-stability test was normal on admission; but, because this could not be repeated, an inherent enzyme defect could not definitely be excluded as contributing to the drug-dependent hæmolysis, since the population of sensitive cells might have been destroyed in the acute hæmolytic episode. As in case 1, however, definite evidence for an autoantibody mechanism was obtained.

Serology

The serological findings were similar to those in case 1. The direct antiglobulin reaction was positive, and it was of the non-γ-globulin type. Two samples of the patient's serum gave the same results. Each sample in the presence of P.A.S. agglutinated normal red cells of the patient's blood-group (titre 16), as well as sensitising them to antiglobulin serum, and also agglutinated and hæmolysed (in the presence of complement) trypsinised normal red cells and hæmolysed P.N.H. red cells (table III). The indirect antiglobulin reaction was almost abolished if the patient's serum was heat-inactivated before sensitisation.

The activity of the antibody was dependent on the presence of P.A.S. and could be demonstrated using final concentrations of P.A.S. ranging from 10 mg. per 100 ml. to 500 mg. per 100 ml. (the highest concentration tested). No abnormal serum activity could be demonstrated in the presence of isoniazid or streptomycin. Drugs chemically related to P.A.S. were next tested. Positive reactions were obtained with sodium salicylate and sodium *p*-aminobenzoate; but the results were negative with sodium benzoate, sodium *p*-aminohippurate, salicylamide, procaine hydrochloride, phenacetin, paracetamol, paraphenetidine, probenecid, and sulphadiazine.

Discussion

These two cases are thought to represent the second recorded instance of an autoimmune type of phenacetin-induced hæmolytic anæmia, and the first report of such a phenomenon due to P.A.S. The association of renal failure with hæmolysis in both cases suggests that the renal damage was secondary to intravascular hæmolysis. This is probable in case 2, but less likely in case 1 because the hæmolysis was mild. As renal damage has been described as a toxic effect of both phenacetin and P.A.S., the drug hypersensitivity in these two patients conceivably led to damage to renal cells as well as to red cells. The clinical course in each was that of acute oliguric renal failure, characteristic of acute tubular necrosis from any cause. In case 1 renal biopsy in the early recovery phase showed only the changes of healing tubular damage—i.e., pigmented casts in the tubules with considerable interstitial cellular reaction (see figure). There was no evidence of a longstanding or recent glomerular lesion. In view of the serious side-effects of phenacetin in certain individuals, it would seem justifiable to omit this drug from the numerous analgesic mixtures available to the general public.

Summary

Of two cases of hæmolysis and acute oliguric renal failure, one followed ingestion of small amounts of phenacetin, and the other treatment with *p*-aminosalicylic acid.

In each case the hæmolysis was shown to be due to the production of an autoantibody, acting on the patient's red cells in the presence of the drug.

The acute tubular necrosis may have been secondary to the hæmolysis. Alternatively, the renal cells may also have been damaged directly as the result of a hypersensitivity reaction.

We wish to thank Prof. J. V. Dacie and Dr. M. D. Milne for their advice and interest in the study of these patients.

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Addendum

Since this paper was written, a case-report of phenacetin-induced acute hæmolytic anæmia, associated with diminished red-blood-cell content of reduced glutathione, has been published (I. B. Houston and A. M. Barlow, *Lancet,* 1959, ii, 1062).

FREEZING-POINT OF HUMAN SKIN

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Lewis and Love (1926) reported that human skin did not freeze until it was cooled to −2·2°C, and could often be supercooled to much lower temperatures. They made these estimates by pressing metal bars cooled to a known temperature on to the skin. Ungley (1949) and McCance et al. (1956) stated, probably on this evidence, that frostbite could not have contributed to the immersion injuries they reported in men immersed in seawater, which freezes at −1·9°C. R. B. Lewis (1951) reported that when the legs of rabbits were plunged into a freezing mixture the deep temperature of their legs stabilised for a time at about −2·2°C, suggesting that this latter was the true freezing-point of the tissues. However, Smith (1954), Lovelock and Smith (1956), and Appelboom et al. (1958) reported that the true freezing-point of mammalian tissues was close to that of blood, which freezes at about −0·55°C (Margaria 1930).

It therefore seemed important to re-examine by a different technique to that of Lewis and Love (1926) the question of whether human skin can freeze at a higher temperature than −1·9°C, the freezing-point of sea water, and to attempt to measure accurately its true freezing-point.

Methods

The little fingers of healthy men and women aged 18–38 were used in all "in-vivo" experiments. In most cases a rubber tourniquet was applied to the base of the finger to stop the circulation, since without a tourniquet changes in blood-flow caused fluctuations in temperature which interfered with the determination of true freezing-point. A thermojunction made from welded 34-gauge copper-and-constantan wire was either applied to the surface of the finger by zinc-oxide plaster, or inserted for a length of 1 cm. into an intracutaneous track made previously in the deeper layers of the epidermis on the pad of the finger by a needle (Keatinge 1957). Another method attempted twice was to strap the two little fingers together, with a thermojunction between them. However, the temperature between the two fingers fell so slowly that the risk of injury due to prolonged freezing of the more exposed parts of the finger made it necessary to abandon these experiments before the freezing-point could be determined. On another occasion a subcutaneous needle thermocouple was used. The cold junction of the thermojunction was in a vacuum flask of distilled water and ice, and the electromotive force was led to a direct-reading galvanometer. This apparatus was calibrated and was accurate to ±0·01°C.

Before most experiments the entire finger, with the thermocouple and tourniquet in place, was cooled in a mixture of ice and water until the temperature of the junction had fallen to near 0°C. This required 10 minutes in most cases and rather longer in others. The purpose of pre-cooling was to reduce the thermal gradients in the finger at the time it was put into the brine, and thereby improve the accuracy of estimation of the true freezing-point of the skin. In many cases, when several layers of plaster were applied to a finger, it was enclosed in a rubber finger-stall during pre-cooling, to prevent fresh water being absorbed by the plaster and disturbing the freezing-point determination. The finger-stall was removed before the finger was put into the brine. The distal phalanx only was then immersed in a freezing mixture of brine and ice. This was in a circular container and was stirred mechanically so that the mixture flowed steadily past the finger. The temperature of the mixture was measured by a mercury thermometer accurate to 0·01°C, and was kept at −1·9±0·02°C by adding salt when necessary.

Results

Freezing of Fingers in Brine at −1·9°C

Fig. 1 shows the temperature recorded from the surface of the pads of the terminal phalanges of W. R. K.'s and P. C.'s little fingers in brine at −1·9°C. In each case the thermojunction was covered by two strips of zinc-oxide plaster 3 mm. in width, circulation to the finger had been arrested by a tourniquet, and the finger had been pre-cooled in ice and water at 0°C for 10 minutes before it was put into the brine. In brine the temperatures at first fell sharply towards that of the brine, but, after 1 minute in the case of P. C. and 1 minute 15 seconds in the case of W. R. K., they rose rapidly to about −1·2°C, remained at this level for about 1 minute, and then drifted slowly downwards again. Each finger was removed from the brine after 7 minutes, and at the end of this time they felt and sounded hard when tapped with a piece of wood.

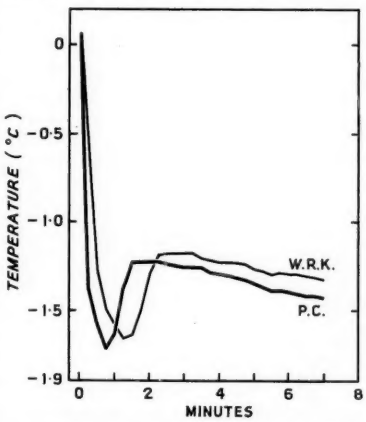

Fig. 1—Surface temperatures of the little fingers of W. R. K. and P. C. in brine at −1·9°C (circulation arrested by tourniquet, thermocouple covered by two layers of plaster).

Table I shows the results of similar experiments on three other men and six women. The procedure in these was identical with that in the experiments on W. R. K. and P. C. except that the fingers were left in the freezing mixture for only 4 minutes in most cases. In all except one case there was a sharp rise in temperature starting 45 seconds to 1 minute 45 seconds after the distal phalanx was immersed in brine, and the fingers were hard to the touch when removed. In one case the temperature fell irregularly, probably due to brine reaching the thermo-

TABLE I—SURFACE TEMPERATURES OF LITTLE FINGERS DURING FREEZING IN BRINE AT −1·9°C

Subject no.	Sex	Lowest temp. reached (°C)	"Plateau" temp. attained (°C)	Start of rise in temp. (min. after immersion)	Appearance of finger at conclusion	Duration of immersion in brine (min.)
1	F	−1·50	−1·22	1·5	Hard, white	4
2	F	−1·43	−1·25	1·5	" "	4
3	F	−1·55	−1·21	1·25	" "	4
4	F	−1·73	−1·01	1·75	" "	4
5	M	−1·40	−1·15	1·0	" "	4
6	F	−1·86	−1·76	0·75	" "	4
7	M	−1·87	−1·53	1·0	" "	4
8	F	*	*	*	" "	7
9	M	−1·64	−1·53	1·0	" "	4
Mean	..	−1·62	−1·33	1·22	..	..

* Surface temperature of this finger fell irregularly, probably owing to plaster allowing brine to reach thermojunction.

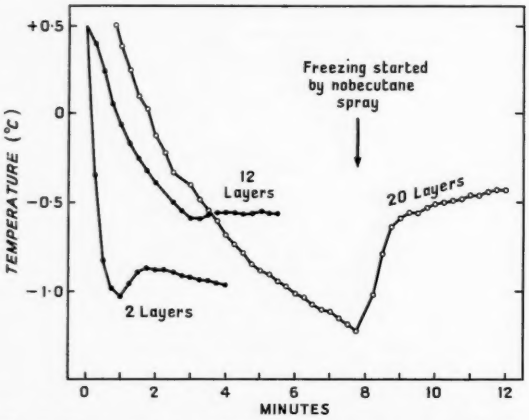

Fig. 2—Temperature recorded from intracutaneous tracks in W. R. K.'s little finger in brine at −1·9°C (circulation arrested by tourniquet, thermocouple and track covered by varying thicknesses of plaster).

junction, but this finger like the others appeared hard, white, and frozen when removed after 7 minutes. The temperature in the other fingers rose to a plateau level usually at about −1·3°C.

True Freezing-point of Skin

Fig. 2 shows the results of three experiments on W. R. K. which were representative of a number made on him and P. C. to try to determine the freezing-point of the skin more accurately. The thermojunction was inserted into an intracutaneous track instead of lying on the surface, and was covered by varying thicknesses of plaster. The finger was pre-cooled in ice and water to near 0°C in every case, and before the experiment with 20 layers of plaster was protected by a rubber finger-stall during pre-cooling in fresh water. With 2 layers of plaster the temperature rose to −0·85°C when the finger started to freeze and then drifted downwards. With 12 layers, the temperature rose to −0·55°C, only slightly higher than the level to which it had fallen, and remained steady. With 20 layers of plaster, the finger did not freeze spontaneously. Freezing was, however, initiated by spraying it briefly with 'Nobecutane', and its temperature rose rapidly to −0·63°C and thereafter drifted upwards more slowly.

Table II shows the results of a number of experiments of this type on W. R. K. and P. C. using an intracutaneous or (in one experiment) a subcutaneous thermocouple in the tip of a needle. In all cases when more than 6 layers of plaster were applied they indicated a freezing-point between −0·53 and −0·65°C, the results for P. C. being rather lower than those for W. R. K. Soaking of W. R. K.'s finger in fresh water for 30 minutes had little effect on its freezing-point. The subcutaneous needle thermojunction used in one experiment on W. R. K. gave a rather lower figure, probably because of stem error.

Supercooling

In all the nine experiments recorded in table I the fingers, which were previously soaked in fresh water and ice, started to freeze spontaneously within 2 minutes of immersion. However, there was always a rise in temperature when freezing started, showing that there had been some supercooling.

P. C.'s little fingers froze spontaneously in brine at −1·9°C, even when they had been protected from fresh water during pre-cooling. W. R. K.'s fingers usually froze spontaneously in brine at −1·9°C when they had been previously soaked in fresh water, but failed to do so on one occasion, and failed to freeze on all five occasions when they were immersed for 8–15 minutes in brine at −1·9°C without preliminary soaking in fresh water. Rubbing a supercooled finger with wood or ice always failed to initiate freezing, but spraying a small part of the skin with nobecutane started freezing on all of the ten occasions on which this was done, presumably by lowering the surface temperature of a small area of skin briefly to a level sufficient to overcome supercooling.

There was never any difficulty in telling when freezing took place. Apart from the sudden rise in temperature the skin suddenly became white in appearance and hard to the touch, with a clear line of demarcation from the non-frozen tissue. There was often also a sudden sharp pain when freezing was started by the spray, though this was usually absent in spontaneous freezing.

Freezing with Circulation Present

P. C.'s little finger was dipped into brine at −1·9°C without any pre-cooling and without a tourniquet. The immersed skin froze hard after 4 minutes.

Injury

The subjects whose fingers were frozen on a single occasion for up to 4 (or, in one case, 7) minutes experienced severe pain during rewarming, but the fingers looked normal and felt virtually normal the next day, and none subsequently became blistered. However, the day after the distal phalanx of W. R. K.'s right little finger was frozen for the fourth time, it became considerably

TABLE II—DETERMINATION OF THE FREEZING-POINT OF SKIN

Subject	Site of thermojunction	Layers of plaster over thermojunction	Whether finger was protected from fresh water during pre-cooling	Start of freezing (min.)	Temperature at onset of freezing (°C)	Temperature after freezing (°C)
P. C.	Intracutaneous	6	No	Spontaneous 2·5	−1·35	−0·65
	,,	12	No	,, 2·25	−0·75	−0·60
	,,	15	Yes	,, 4·5	−1·40	−0·62
	,,	20	Yes	,, 2·5	−0·94	−0·64
	Mean	..	..	..	−1·11	−0·63
W. R. K.	Shallow subcutaneous	0	No	Spontaneous 2·0	−1·50	−0·81
	Intracutaneous	2	No	,, 1·25	−1·03	−0·87
	,,	6	No	,, 3·25	−0·84	−0·59
	,,	12	No	,, 3·5	−0·59	−0·55
	,,	10	Yes	Spray 2·75	−0·68	−0·60
	,,	10	Yes	,, 2·5	−0·80	−0·56
	,,	10	Yes *	,, 2·5	−0·84	−0·53
	,,	20	Yes	,, 7·75	−1·22	−0·63
	Mean (only experiments with 6 or more layers of plaster included)		..	..	−0·83	−0·58

* Finger soaked for 30 minutes in distilled water, then mopped dry, before thermojunction was inserted in track and plaster applied. Procedure and track were otherwise identical with the previous experiment.

painful and hyperæmic (fig. 3). The hyperæmia and tenderness subsided during the next 4–5 days, but during the next 2 weeks most of the skin on it blistered off. Lesser degrees of hyperæmia and blistering were observed after repeated freezing of W. R. K.'s left little finger and P. C.'s little fingers. The more severe degrees of hyperæmia and tenderness were produced only when a finger was frozen at a time when it was still slightly tender as

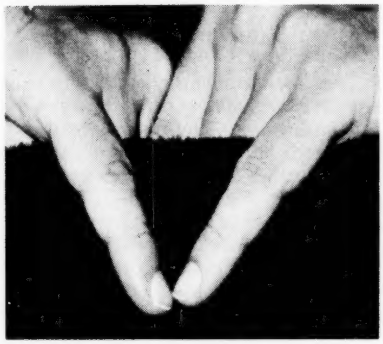

Fig. 3—Appearance of W. R. K.'s right little finger after repeated short periods of freezing in brine at −1·9°C.

a result of an earlier freeze, although the fingers were not frozen more often than once a day, or for more than 8 minutes at a time.

To determine whether the damage was really a result of freezing, or whether it was a result of low temperature per se, an additional experiment was performed on W. R. K. and subject 7.

The terminal phalanx of the left little finger of each of them was supercooled in brine at −1·9°C, with circulation arrested, for 15 minutes, and in each case was still soft at the end of the experiment. On the same day the right little finger of each was also cooled in brine for 15 minutes. the procedure being identical except that, after $3^1/_2$ minutes in the brine, freezing was started by a nobecutane spray. The finger froze immediately; and at the end of the experiment, 11 minutes later, felt very hard. Neither of subject 7's or W. R. K.'s little fingers had been frozen in the 3 weeks before this experiment. The fingers were rewarmed by running water at 15°C over them at the end of the experiment, and care was taken not to subject them to trauma until they had been rewarmed.

The next day the fingers which had been supercooled looked and felt normal, while the fingers which had been frozen were tender and red and their skin temperatures were 4–8°C higher than those which had been supercooled. The tenderness and difference in skin temperature decreased and had virtually disappeared 5 days later.

Discussion

These results show that, contrary to general belief, human tissues can freeze at the temperature of freezing sea-water and that they can sustain injury as a result of being frozen at this temperature.

Lewis and Love (1926) were unable to freeze human skin by placing it in contact with metal at temperatures above −2·2°C, and Lewis (1941) stated that " freezing of feet while immersed in sea water can hardly occur for the temperature of the water cannot fall below −1·9°C, its own freezing point ". This apparent discrepancy with the present findings is probably due to the difference in method; large temperature gradients must exist in the skin when a metal bar is pressed on the skin of a warm limb, and even the most superficial part of the skin must be at a higher temperature than the bar. Lewis and Love (1926) observed that supercooling of skin was common and could be reduced by soaking the skin in fresh water. The present experiments confirm this; dry fingers sometimes supercooled and sometimes froze in brine at −1·9°C, but they almost always froze when they had been soaked in fresh water beforehand. They failed to do so on only one occasion after such preliminary immersion.

In the experiments with surface thermocouples covered by two layers of plaster their temperature rose to −1–−1·76°C when the skin froze. Since the thermocouples were between the skin and the brine, the temperature they recorded must have been below that of the skin; and the true freezing point must have been higher. The experiments using intracutaneous tracks and 6–12 layers of plaster, on the other hand (table II, fig. 2) gave stable temperatures for some minutes in the region −0·6°C when freezing started. When more layers of plaster were applied the temperature failed to stabilise after the sudden rise when freezing started, and continued to drift upwards, probably because the junction lay in a region between the freezing tissue and the warm, non-immersed part of the finger. The position of the breaks in these curves also, however, indicates a true freezing-point of about −0·6°C.

No previous determination of the true freezing-point of human skin appears to have been made; Lewis and Love (1926) were clear that their method determined the temperature at which supercooling was overcome rather than the true freezing-point, which must be higher. The freezing-point of mammalian tissues has been reported to be −2·2°C (R. B. Lewis 1951), but Lovelock and Smith (1956) and Appelboom et al. (1958) have found it to be about −0·56°C. This is approximately the freezing-point of blood, which may vary from −0·51 to 0·61°C with varying degrees of hydration of the body (Margaria 1930). It is a familiar observation that human skin becomes wrinkled when soaked in fresh water, and must therefore absorb water which will raise its freezing-point somewhat. Such absorption of water by the surface layers may reduce the power of skin to supercool (Lewis and Love 1926, table II), but since only a trivial elevation of freezing-point, within the limit of experimental error, could be obtained by soaking for 25 minutes (table II), the freezing-point at least of the deeper layers of the skin cannot have been greatly altered by these means.

It might be argued that cold vasodilatation should normally protect the extremities from freezing in brine at −1·9°C. However, although cold vasodilatation always appears eventually in the fingers of even chilled men when the fingers are cooled to 0°C, the dilatation always takes several minutes, and often 30 minutes or more, to start (Keatinge 1957). The extremities can clearly freeze solid long before this time, and freezing of P. C.'s little finger was observed 4 minutes after immersion in brine at −1·9°C even without previous cooling and with the circulation intact.

Although freezing at −1·9°C for periods of 4–7 minutes did not give rise to any significant after-effects, freezing for $11^1/_2$ minutes caused pain and hyperæmia for several days. Repeated freezing for shorter periods at intervals of a day or two caused pain, hyperæmia, and blistering of the skin. Lewis and Love (1926) reported

that freezing of human skin caused more injury than supercooling; but Smith (1954) reported that supercooling, as well as freezing, could cause necrosis of the extremities of hamsters. Since supercooling of fingers in these experiments did not cause the after-effects produced by freezing them at the same temperature and for the same time, and since on previous occasions fingers have been kept at 0°C for much longer without injury (Keatinge 1957), the change observed in these fingers must have been due to freezing. The results obtained by Smith (1954) in hamsters suggest that the injury would have been greatly increased if the tissue had been subjected to trauma while frozen; trauma to frozen fingers was carefully avoided in the present experiments.

The greater injury caused by repeated freezing in these experiments contrasts with the report of Fuhrman (1957) that a brief freeze of the legs of rats (1 second at −25°C) decreased the damage caused by subsequent freezing 2 days later. The difference in the duration and temperature of freezing in this worker's experiments, and the fact that rats were used, may account for the apparent contrast with the present results.

The freezing-point of sea-water in the Arctic Ocean is variable, particularly near the mouths of Arctic rivers, but in the region of the Norwegian sea, as in most of the ocean, it is about −1·9°C (Sverdrup et al. 1942). Many immersion injuries were suffered by men in ships sunk in this area in the late war (Ungley 1949, McCance et al. 1956). The present results show that frostbite may contribute to such injuries and is particularly likely if the skin is wet before immersion. It is clearly important to provide sufficient protection to keep the skin temperature 1°C or more above water-temperature when immersion in freezing sea-water is unavoidable.

Summary

Human fingers cooled to −1·9°C, the freezing-point of sea-water, usually froze. They almost invariably did so when they had been soaked in fresh water and ice beforehand.

The true freezing-point of human fingers was found to be between −0·53 and −0·65°C.

Freezing in brine at −1·9°C for 4–7 minutes, without trauma in the frozen state, caused no significant injury. However, freezing for $11^1/_2$ minutes or repeated freezing for shorter periods caused hyperæmia and tenderness lasting several days and, in the case of repeated freezing, blistering of the skin. No ill-effects were produced by supercooling fingers to the same temperature for the same time.

Earlier statements that human tissues cannot freeze in sea-water appear to have been based on indirect evidence.

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FÆCAL LOSS OF FLUID, ELECTROLYTES, AND NITROGEN IN COLITIS BEFORE AND AFTER ILEOSTOMY

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A WELL-RECOGNISED danger of ulcerative colitis is considerable depletion of fluid and electrolytes from excessive gastrointestinal loss. This may arise either because of severe diarrhœa in the intact patient undergoing medical treatment, or because of profuse postoperative discharge from the ileostomy. The magnitude of the loss in each of these circumstances has been specially studied by Lubran and McAllen (1951) and Crawford and Brooke (1957). These workers have stressed particularly the risk of potassium deficiency in the medically treated colitis patient who still has a functioning large intestine, and of sodium depletion after an ileostomy has been established. The investigations which we here report were undertaken as an amplification of this previous work; but our findings, though largely confirmatory, differ in certain important respects.

Material and Methods

Fæcal loss of fluid, sodium, potassium, and, in certain circumstances, nitrogen was estimated in nine patients awaiting operation for ulcerative colitis, and in sixteen patients after operation, which in all cases took the form of a one-stage ileostomy with total proctocolectomy. Similar investigations were made in two cases with ileostomies established for 12 months. Three of the preoperative patients and the two patients with established ileostomies were given an ordinary ward diet, but six had extensive balance studies, being given various quantities of sodium and potassium with a fixed intake of 3000 ml. water daily.

In most of the postoperative cases the fluid and electrolytes given accorded with the needs of ordinary postoperative management. Intravenous infusion was continued as a rule for only 24–36 hours. Fluids were given by mouth immediately after operation, and were gradually increased in amount from 30 ml. hourly until, by the 4th or 5th postoperative day, a light diet was taken, and by the 8th–12th days the diet was fairly full. In three patients, however, a fixed intake of 3000 ml. of fluid daily, together with sodium 300 mEq. and potassium 87 mEq., was maintained throughout the period of investigation—i.e., up to the 12th postoperative day.

Of the sixteen patients studied after operation all except one recovered without complicaton. Six had steroid therapy during and after operation (dosage: 100 mg. t.d.s. for 2 days, 100 mg. b.d. for 2 days, and then reduction of the total dose by 50 mg. daily to a maintenance dose of 50 mg. daily, which was continued until the end of the study period). Of these six patients, five recovered uneventfully, but in one peritonitis necessitated further operation to drain the abdomen. After this she progressed satisfactorily, although profuse ileostomy diarrhœa was associated with the intraperitoneal sepsis.

Collection of Specimens and Chemical Analysis

24-hour collections of urine and fæces or ileostomy fluid were made. Each specimen was measured for volume, and analysed for sodium, potassium, and nitrogen content.

Volume of fæces or ileostomy fluid.—The specimen was transferred to a graduated volumetric flask, using a weighed amount of water, and filled to the mark with a weighed amount of water. (Thus: volume of specimen = volume of flask − weight of water added.) The contents of the flask were then homogenised. If frothing appeared, a few drops of caprylic alcohol were added.

Sodium and potassium estimations.—To 10 ml. of the homogenised "fluid" in a conical flask concentrated nitric acid 2 ml. (analytical reagent) was added. (The acid had previously been freed from all lower oxides of nitrogen by boiling with $^1/_4$ of its volume of water until the brown discoloration disappeared.) With a glass bubble in the top of the flask, the mixture was brought to the boil for a minute or two. After cooling, the digest was transferred to a 50 ml. graduated flask. The volume was made up to the mark with distilled water, and the contents were mixed thoroughly. The mixture was filtered, and the filtrate was diluted similarly with water. The sodium and potassium contents were measured in an 'Eel' flame-photometer.

Nitrogen estimation.—The macro-Kjeldahl method was used. 10 ml. of homogenised fæces or ileostomy fluid or 5 ml. of urine was digested with concentrated sulphuric acid 20 ml. and copper sulphate 0·2 g. in a 250 ml. Kjeldahl flask. Heating was continued for 1 hour after the colour had cleared. After cooling, distilled water 80 ml. was added, followed by caustic soda 40% in excess (phenolphthalein indicator). The ammonia was distilled over into 0·2 *N* sulphuric acid 20 ml., containing methyl-red as indicator. When the volume of the liquid in the Kjeldahl flask had been reduced by half, distillation was discontinued. The excess acid in the receiving flask was titrated with 0·1 *N* sodium hydroxide, and the nitrogen content was then estimated.

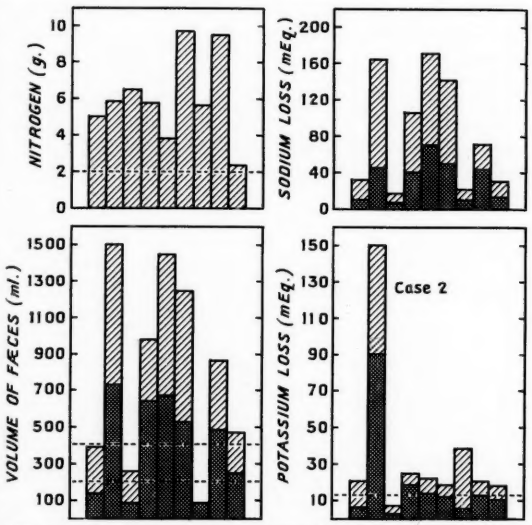

Fig. 1—Daily minimum and maximum fæcal volumes and sodium, potassium, and nitrogen loss in nine colitis patients before operation.

Results

BEFORE OPERATION

Volume of fæces.—Fig. 1 shows the minimum and maximum fæcal volumes in the nine patients investigated before operation. The normal maximal fæcal volume of 400 ml. was exceeded in all except two. In three patients the fluid intake was increased from 1500 ml. to 3000 ml. per day, without increase in fæcal volume. But when the fluid and sodium intakes were increased simultaneously the fæcal volume rose rapidly.

Sodium excretion.—Accepting the normal fæcal loss of sodium as 2–5 mEq. per day, the results in all the patients studied (fig. 1) show that the excretion was greatly in excess of normal. Although the sodium loss varied between 9 and 170 mEq. per day, in no patient was this sufficient to produce the clinical syndrome of sodium depletion. In six patients (cases 4–9), in whom the fluid intake was 3000 ml. daily, the sodium intake was known. The table shows the effect of a higher sodium intake (cases 7–9) on the fæcal and urinary volumes and the fæcal and urinary excretion of sodium. (These data were compiled after an initial period of 6 days for equilibration.)

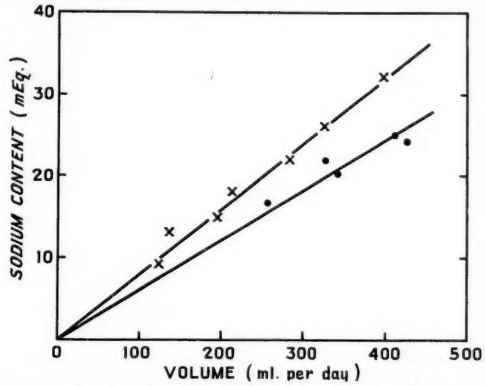

Fig. 2—Sodium loss in two of the seven patients in whom sodium excretion was proportional to fæcal volume.

When increased quantities of sodium were taken by mouth both the sodium content and volume of the fæces increased; this may indicate a defective absorptive capacity of the large bowel for sodium. In seven of the nine patients investigated the sodium excretion was proportional to the fæcal volume (fig. 2). Though the sodium content of the fæces was remarkably constant in any one patient despite considerable fluctuations in volume, the amount of sodium varied from patient to patient.

Potassium excretion.—As fig. 1 shows, the loss of potassium exceeded the normally accepted value of 6–12 mEq. per day in all except one patient. With this exception the potassium loss was relatively little, being only 2–3 times the average daily normal. In this patient (case 2, column 2) the loss of potassium varied between 90 and 167 mEq. per day, but despite this (and without potassium supplements by mouth) the serum-potassium level remained within normal limits. In five patients the

SODIUM EXCRETION IN COLITIS PATIENTS ON LOW AND HIGH SODIUM INTAKE

—	Case no.					
	4	5	6	7	8	9
Daily intake of sodium (mEq.):						
Day 1	103	92	110	237	277	334
„ 2	103	92	110	237	277	334
„ 3	103	92	110	237	277	334
„ 4	103	92	110	237	277	334
„ 5	103	92	110	237	277	334
„ 6	103	92	110	237	277	334
Daily fæcal excretion of sodium (mEq.):						
Day 1	18	66	23	49	71	95
„ 2	15	60	25	83	70	65
„ 3	14	57	25	108	90	99
„ 4	9	53	20	114	40	120
„ 5	9	60	16	123	108	148
„ 6	18	52	24	144	..	170
Fæcal volume (ml.):						
Day 1	488	825	319	515	781	870
„ 2	89	676	411	662	830	692
„ 3	312	624	426	1092	895	920
„ 4	232	590	338	1072	619	1030
„ 5	181	693	251	1000	940	1359
„ 6	306	604	481	1225	..	1472
Daily urinary sodium (mEq):						
Day 1	91	4	56	202	175	209
„ 2	69	7	86	..	164	248
„ 3	114	10	88	157	172	148
„ 4	91	13	82	116	172	150
„ 5	97	16	80	59	105	84
„ 6	99	17	72	61	206	103
Daily urinary volume (ml.):						
Day 1	2014	635	1106	920	1200	1900
„ 2	1850	1220	1600	..	850	1430
„ 3	2050	1100	1470	860	1400	1250
„ 4	2035	1110	1670	700	955	1220
„ 5	2048	720	1770	580	845	878
„ 6	2280	1350	1470	640	1270	1300

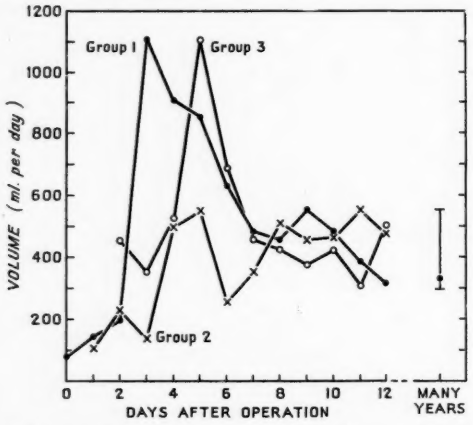

Fig. 3—Volume of ileostomy discharge in the 3 groups of patients not treated with steroids.

fæcal potassium loss was related directly to volume, but, as with the sodium loss, this was not applicable to the group as a whole, neither did potassium loss and fæcal volume necessarily correlate in those patients in whom sodium loss correlated with the volume of fluid excreted.

Nitrogen excretion.—In seven patients in whom the fæcal nitrogen loss was studied, the normal value of 2 g. per day was exceeded. This caused the fæcal nitrogen loss to fluctuate between 20% and 30% of the daily intake of protein, compared with the normal of 10%. Four of the six patients subjected to balance studies (daily nitrogen intake 9·4–12 g.) were in negative balance—a result in keeping with their progressive weight loss.

AFTER OPERATION

Uncomplicated Cases not having Steroids

The eleven patients have been divided into 3 groups depending on the time of onset of ileostomy discharge after operation. In group 1 (two patients) the discharge started on the day of operation, in group 2 (four patients) it began on the 1st day after operation, and in group 3 (five patients) it was delayed until the 2nd day.

Volume of ileostomy discharge.—The average volume of ileostomy discharge in the 3 groups is shown in fig. 3.

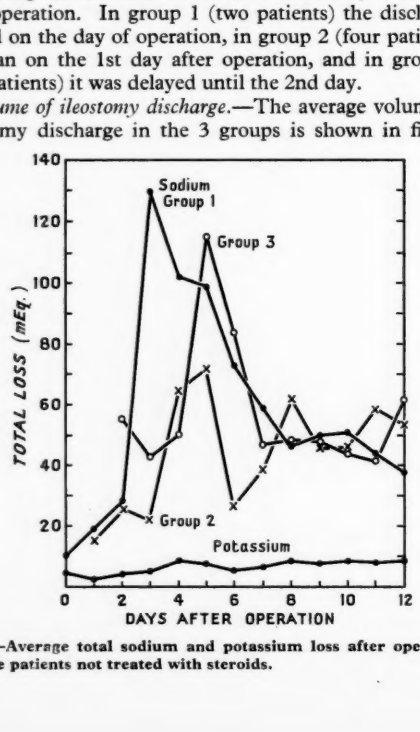

Fig. 4—Average total sodium and potassium loss after operation in the patients not treated with steroids.

After the ileostomy began to function the volume of discharge increased rapidly until, between the 3rd and 5th days, a maximum was reached. The volume then diminished until, by the end of the 1st week, the volumes excreted were within the range of the established ileostomy—i.e., between 200 and 500 ml. per day. After the period of greatest excretion the consistence of the ileostomy discharge rapidly changed until, by the end of the first 10 days, it was porridge-like, resembling the fæces from a long-established ileostomy. In only two patients was the volume of discharge more than 2000 ml. per day, and this abnormal amount was passed once only in each case.

Sodium.—The daily average sodium excretion via the ileostomy was calculated for each of the 3 groups. The total loss of sodium did not exceed 130 mEq. per day in any patient, and the greatest loss of sodium corresponded to the greatest discharge from the ileostomy. In all patients within 1 week of operation the daily sodium loss fell to 40–60 mEq., a rate of excretion such as is found with long-established ileostomy. Fig. 4 shows the average daily loss of sodium for each group. Comparison with fig. 3

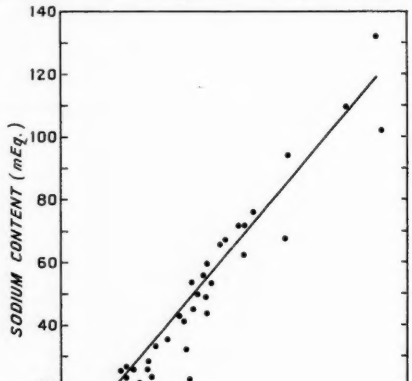

Fig. 5—Relation between sodium content and volume of ileostomy fluid in patients not treated with steroids.

suggests that sodium and fluid loss are closely related; indeed these two factors are directly proportional, as is shown in fig. 5, calculation of their correlation coefficient exceeding the 0·1% level of significance. Thus the sodium content of the ileostomy fluid seemed to remain constant at 120 mEq. per litre when volumes within the normally accepted range were excreted.

Potassium.—The total potassium loss varied between 1 and 12 mEq. daily. But whereas the correlation between sodium content and fluid excreted satisfies all statistical inquiry, this was not true of potassium, the loss of which varied from day to day within very narrow limits.

Nitrogen.—Nitrogen excretion from the ileostomy was negligible in the seven patients in whom it was measured. The amount varied between 0·4 and 1·8 g. daily, these values representing the minimum and maximum values over a period of 15 days' observation. The loss of nitrogen is thus not important in the practical management of ileostomy patients.

Cases treated with Cortisone

The following data relate only to the postoperative period. Cortisone seemed to exert an influence on both

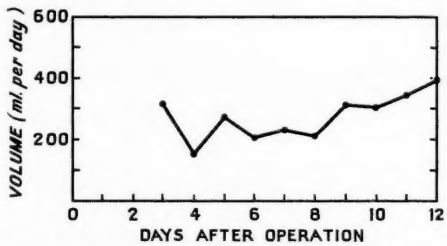

Fig. 6—Average volume of ileostomy discharge in five cortisone-treated patients.

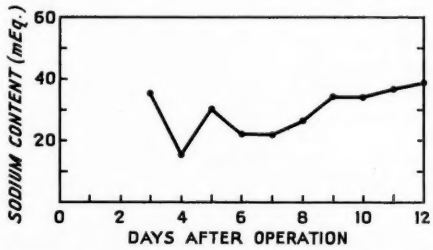

Fig. 7—Average total daily sodium loss in five cortisone-treated patients.

the quantity of the ileostomy discharge and the concentration of its constituents.

Volume.—The time-interval between operation and the onset of ileostomy function was uniformly delayed until the 3rd postoperative day in patients treated with cortisone. Fig. 6 shows that, whilst the volume of the ileostomy discharge ultimately reached that typical of the patients who did not have steroids, no peak of excretion appeared in the early postoperative period.

Sodium excretion.—The total daily sodium excretion in the five patients investigated is shown in fig. 7. The greatest total loss of sodium in a single case in this group was 87 mEq. per day, but in the whole group, in which 100 observations were made, only 10 values exceeded 50 mEq. per day. As with fluid excretion there was no peak of sodium excretion. The sodium content of the discharge was 109 mEq. per litre as compared with 120 mEq. per litre in the patients not treated with steroids—a statistically significant difference.

Potassium.—The total potassium loss via the ileostomy varied between 3 and 9 mEq. per day, these values being similar to those observed in the cases not treated with cortisone. The total potassium loss increased with the volume of the discharge and then remained relatively constant.

Nitrogen.—Loss of nitrogen from the ileostomy was specifically investigated in one patient only, but, since values between 0·5 and 1·7 g. per day were found, the loss of nitrogen is probably similar to that previously observed in the patients not treated with steroids.

Ileal Dysfunction Associated with Peritonitis in a Patient having Steroids

In one patient ileal dysfunction was apparently due to intra-abdominal sepsis. When the abdomen was re-explored on the 4th postoperative day general peritonitis was found, and the abdomen was drained; after a difficult convalescence the patient recovered. The total fluid, sodium, and potassium loss in this case are recorded in fig. 8. This shows the greatly increased volume of fluid excreted throughout the period of observation, and the high loss of sodium and potassium amounting to as much as 300 mEq. of sodium and 60 mEq. of potassium daily. Whilst the sodium content fell below the normal of 120 mEq. per litre, the potassium content was abnormally high. In such circumstances there is danger of both sodium and potassium depletion, and intravenous supplements of these cations were required throughout the period of investigation.

The changes in the ileostomy discharge in this case seem to us characteristic. Indeed another patient in whom peritonitis developed on the 18th postoperative day had similar changes in the ileostomy discharge, although the chemical data were insufficient for us to report this case in detail.

Discharge from the Long-established Ileostomy

In two patients whose ileostomy discharge was investigated some time after the fistula was established the results agree with those already described during the 2nd week of function in patients not having steroids.

In both our patients the total daily volume of discharge fluctuated between 300 and 500 ml. The sodium content agreed closely with the previous findings, being 120 mEq. per litre. The potassium loss ranged from 3 to 4·8 mEq. per day, and even in the same patient the content varied.

The nitrogen loss differed little between the patients with recently established and long-established ileostomies, values between 0·5 and 2 g. daily being observed in the latter.

Discussion

The Preoperative Patient

Contrary to the reports of Gardner et al. (1949) and Lubran and McAllen (1951) potassium deficiency was not a problem in the preoperative management of the seven patients we studied in detail (neither was lack of potassium a notable feature in ninety-eight additional cases which came under our care for surgical treatment during the past 4½ years, being evident in only two of these patients). This is perhaps surprising in view of the earlier findings of potassium depletion in four out of thirty consecutive cases of colitis observed by Lubran and McAllen (1951). But in our cases the fæcal volumes were relatively small, never being greater than 1500 ml. per day, whereas

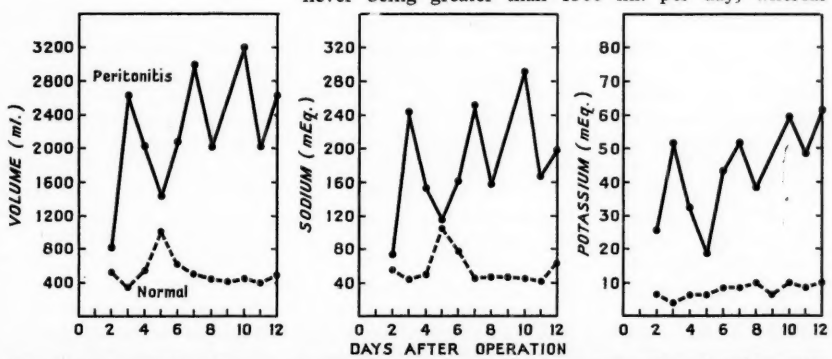

Fig. 8—Loss of fluid, sodium, and potassium in a patient with gross intraperitoneal inflammation compared with the "normal".

in Lubran and McAllen's patients the daily loss of fluid per rectum was as much as 2500 ml. Welch et al. (1937) and Lubran and McAllen (1951) found that electrolyte loss was determined by the fæcal volume. Welch et al. found that the sodium and potassium loss in colitis patients was (jointly) equivalent to a 70% isotonic solution; Lubran and McAllen thought the fæcal fluid was isotonic with plasma.

Our findings suggest that the cation equivalent of the fæces varies, ranging from hypotonic to isotonic in different patients and from day to day, depending on fæcal bulk. Lubran and McAllen (1951) found that the loss of sodium and potassium was directly proportional to the volume of fluid excreted. But in our experience, though the loss of cations may be proportional to the volume, the observations in one patient are not applicable to the next, neither is a proportional potassium loss necessarily found in patients with a fixed relation for sodium.

Our findings suggest also that in colitis the inflamed colon is unable to absorb sodium, for when increased amounts of sodium were given by mouth increased quantities were lost in the stools, which were of greater volume.

In general the loss of nitrogen in the colitis patient is higher than normal, as shown by the increased fæcal loss. The greatest fæcal loss of nitrogen in any of the seven preoperative patients we studied was 10 g. per day (roughly equivalent to 60 g. of protein), exceeding greatly the normal of 2 g. per day. Miller et al. (1949) alleged that a fæcal loss of up to 100 g. of protein daily might arise in severe cases of colitis, and therefore favoured primary colectomy instead of simple ileostomy, leaving the colon intact. Whilst we cannot confirm their estimations, we think that a sustained daily loss of 60 g. of protein could be seriously detrimental, particularly postoperatively, when intake might be much reduced.

The Ileostomy Patient

Our findings regarding sodium excretion from the recently formed ileostomy are notably at variance with those of Crawford and Brooke (1957). These workers claimed that immediately after the establishment of an ileostomy the fæcal sodium content was at first very high, amounting to 200–400 mEq. per litre, and that as the fæces gradually thickened the sodium content fell to the same level as is found in patients with long-established ileostomies—namely, about 150 mEq. per litre. But if this initial value were added to the potassium loss of 10 mEq. per litre which they found, a hypertonic fluid would be excreted via the recently established ileostomy. This would be somewhat remarkable. Apart from conflicting with our findings, it conflicts also with the findings of Lans et al. (1952), who estimated, by aspirating the ileal contents through nasal or oral tubes, that the sodium content was about 121 mEq. per litre (range 88–146 mEq.) and the potassium content 9·6 mEq. per litre (range 4·8–13·6 mEq.), which implies that the ileostomy discharge should be isotonic or slightly hypotonic relative to plasma.

Crawford and Brooke (1958) admitted later that the high sodium content they had found in the ileostomy fluid immediately after operation was difficult to understand. After a careful check on their methods they suggested a possible explanation. All their patients were given sodium-chloride tablets by mouth after operation, and some of these might not have dissolved completely in the alimentary tract, thus being passed semidigested and dissolving later in the storage cans, thereby raising the sodium content.

We found that in most patients ileostomy function began on the 2nd day after operation, that the greatest fæcal volume was excreted during the 1st week, and that the volume of discharge was then in most cases equivalent to the accepted normal for the established stoma. The maximum volume was seldom greater than 1000 ml. per day in the absence of complications, and we believe that if greater volumes than this are excreted the ileostomy is malfunctioning, either because of mechanical difficulties, such as obstruction, or because of inflammatory changes close to the bowel, as in peritonitis.

In all our patients the sodium loss seemed to be directly proportional to the volume excreted, and in the average ileostomy patient *the sodium content was 120 mEq. per litre regardless of the fæcal volume.* Thus for practical purposes there is no difference in the concentration of sodium between the recent and long-established ileostomy. Whilst sodium loss was directly related to the volume of ileostomy fluid, the loss of potassium varied between different patients and in the same patient from day to day, but under normal circumstances it never exceeded 11 mEq. per day, which is considerably less than the normal daily intake of 50–200 mEq. potassium (Thompson and King 1957). Thus in the ordinary patient after ileostomy the sodium and potassium loss is not a serious hazard, the volumes excreted are normally small, and the cation contents are together equivalent to a fluid isotonic as compared with plasma.

In the practical management of uncomplicated cases the potassium loss may be ignored completely, and the sodium and fluid loss can be replaced accurately by normal saline (156 mEq. of sodium per litre) intravenously in amounts equal to the volume of ileostomy fluid excreted. But when some condition causes massive increase in the ileostomy discharge, the loss of water, sodium, and potassium may become critical. In our case in which ileal dysfunction was due to peritonitis, the volume of fluid was sometimes as high as 3 litres per day, and never less than 2 litres per day for 14 days during the recovery period. Associated with the high fluid output the total loss of sodium and potassium was considerable—between 260 and 300 mEq. per day for sodium and between 20 and 60 mEq. per day for potassium. This single case suggests that the small intestine makes some attempt to conserve sodium, for when there was profuse ileostomy diarrhœa the fæcal sodium content was reduced to 110 mEq. per litre compared with the normal of 120 mEq. per litre in uncomplicated cases.

The Effect of Cortisone

Many patients with ulcerative colitis have had steroid therapy before surgery, and they therefore need it during and after operation to guard against adrenal failure. Such hormone administration affects the ileostomy discharge.

In 1958 Brooke reported the effect of cortisone on the ileostomy in three patients who had had this drug before and immediately after the stoma was established. He found that cortisone reduced the volume of fluid excreted via both the kidney and the stoma, that the sodium content was lowered, and that the potassium content was raised. In general these findings are confirmed by our present study, the sodium/potassium ratio of the ileostomy fluid (normally 11–18 in patients with a recent ileostomy) being 6 in the cortisone-treated patients. This reduction is due to diminution of the sodium content and increase of the

potassium content of the fæces. That this is not due to chance is shown by the effect of cortisone given temporarily to a patient with an adrenal crisis (fig. 9); in this case the sodium/potassium ratio fell from 16 to 2 after cortisone was given, and rose rapidly again when cortisone was discontinued.

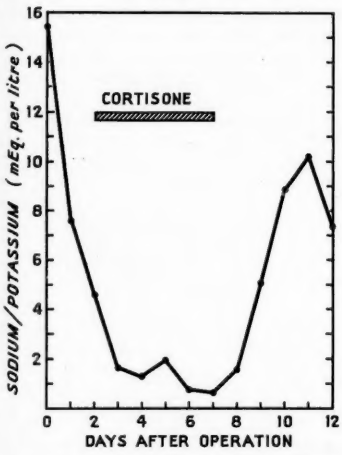

Fig. 9—Effect of cortisone on the sodium/potassium ratio of the ileostomy discharge in a patient with adrenal failure.

Like Brooke (1958) we found that, in general, the volume of ileostomy fluid is lowered in the cortisone-treated patient. Brooke suggested that cortisone might be tried in those patients who normally have a watery ileostomy discharge in the absence of mechanical disturbances of the stoma. But in the one patient we studied with this state of affairs, the volume of the ileostomy fluid did not decrease significantly over a period of 14 days' cortisone therapy. Thus steroids are not always effective in checking such excessive ileostomy action.

Summary

The fluid, electrolyte, and nitrogen loss was studied in nine patients with ulcerative colitis before operation and in sixteen patients after operation.

Before operation the fæcal loss in all patients exceeded the normal, although the loss of potassium was not as high as was expected from the results of previous investigations.

After operation the greatest excretory activity when the volume of discharge rose to as much as 1500 ml. was during the 1st week. The sodium content of the discharge was 120 mEq. per litre, but the potassium content varied. Nitrogen loss varied between 0·4 and 1·8 g. daily.

In patients treated with cortisone postoperatively the volume of the discharge gradually increased to normal values, without a peak. The sodium content was 109 mEq. per litre, and relatively large amounts of potassium were excreted.

In a patient with peritonitis the loss both of fluid and cations was increased considerably, necessitating continuous intravenous supplements throughout the period studied.

We wish to acknowledge with thanks a helpful exchange of ideas with Dr. N. F. Coghill, Dr. M. Lubran, and Mr. B. N. Brooke before we started this study. We are also much indebted to Miss F. E. Briggs, B.SC., dietitian; and to Sister Margaret Thwaites, Sister E. L. Moxon, and Sister Joan Womersley and their nurses for much assistance with this investigation.

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ARTERIAL PERFUSION IN THE LOWER LIMB AS AN AID TO VASCULAR SURGERY

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THE value of restorative procedures in the treatment of obstructive disease of the aortic bifurcation and iliac, femoral, and popliteal arteries is well established. These procedures may take the form of restoring the arterial lumen (disobliteration) or a bypass of the obstruction with arterial homografts or synthetic tubes.

Selection of Patients for Restorative Surgery

There are two main groups of patients: (*a*) those in whom loss of the limb is inevitable in the immediate future, because of gangrene or intolerable rest pain; and (*b*) those in whom the clinical features, claudication, or ulceration are not so clamant, who can carry on even if only with reduced activity. This second group includes some who find restriction of activity intolerable or impossible owing to financial or business reasons, and who should, for the purpose of treatment, be classed with group (*a*).

When assessing each patient for the advisability of restorative surgery the morbidity, mortality, and likely success of the operation must be balanced against the degree of local disability and the general state of the patient. For patients in group (*a*) there is nothing to be lost by an attempt at some restorative procedure, whereas in group (*b*) the problem is more difficult, for gangrene may be precipitated by an unsuccessful operation. When advising patients in this group the position must be put to them squarely without minimising the risks. Cardiac, cerebral, or other disease in an acute phase contraindicates any lengthy operation involving a certain amount of hæmorrhage. A past history of coronary thrombosis is not necessarily a contraindication, though ironically enough a successful operation in a patient with valvular heart-disease may precipitate cardiac failure by reason of the increased cardiac output required.

Arteriography as an aid to diagnosis and selection is indispensable: without it the surgical alternatives are sympathectomy (so capricious in its effects) and amputation. Arteriography reveals the precise site and extent of any arterial obstruction, whether the lesion is multiple, the degree of the collateral circulation, and the patency of the smaller vessels in the lower leg and foot. Restorative operations are only suited to those cases where the principal cause for the ischæmia is in the main vessels and where the distal part of the popliteal artery is sufficiently patent to enable a satisfactory anastomosis of a bypass graft to be effected. In most cases similar disease is present in the smaller vessels, and in some the poor filling of arteries with the contrast medium ('Hypaque') below the knee may be such as to discourage an attack on the main vessel. Table I shows how 44 patients seen in a period of six months were assessed after arteriography.

Measures to Avert Failure in Grafting

In the operative and immediate postoperative period an artery graft will fail if the blood within it clots. Such clotting is the result of poor linear flow. Assuming that the

TABLE I—ANALYSIS OF TREATMENT OF 44 PATIENTS ADMITTED WITH PERIPHERAL VASCULAR DISEASE OF THE LEGS OVER A SIX-MONTH PERIOD

	No.
Operations:	
Amputation	7
Disobliteration	6
Graft	7
Sympathectomy	3
Other	2
No restorative operation attempted:	
Suitable for restorative procedure but risks unjustifiable: "too good" for restorative procedure	13
Local arterial disease too extensive or systemic disease prohibitive: "too bad" for restorative procedure	8

anastomosis (end-to-side) between each end of the graft and patient's artery is technically satisfactory and therefore fully patent, the cause of failure is to be looked for in the blood-flow in the femoral artery above and the popliteal artery below.

1. If there is narrowing of the femoral artery or yet another obstruction above, the impelling force or head of pressure of blood entering the graft is insufficient. Because of this danger it has become the practice over the past three years to join the upper end of the graft to the common femoral or external iliac artery, and *not* to the femoral artery below the origin of the profunda femoris. Thus much longer lengths of graft material (homografts) are being used than before in femoropopliteal obstructions. The head of pressure may be further reduced by operative and postoperative hypotension, measures against which include adequate blood replacement. By opening up collateral channels, sympathectomy will also rob the graft of its blood-flow.

2. Below the distal anastomosis there must be sufficient lumen in the popliteal artery and its branches to admit and pass on towards the foot the full flow of blood from the graft. As evidence of this we have come to rely upon a good "bleed-back" when the popliteal artery is opened. But failure can still occur because, as arteriography often shows, the patency of the posterior and anterior tibial arteries is imperfect. Also any lumen is further reduced by clotting during the period of limb ischæmia that is necessary while the graft is being sewn into position. Prolonged ischæmia causes muscle damage and œdema, and this in turn will obstruct small or partially blocked vessels. Heparin can be administered systemically, but usually it is injected locally as heparin saline down the popliteal artery during grafting. Owing to difficult situations caused by hæmorrhage and hæmatoma formation, systemic anticoagulation is not continued after the operation.

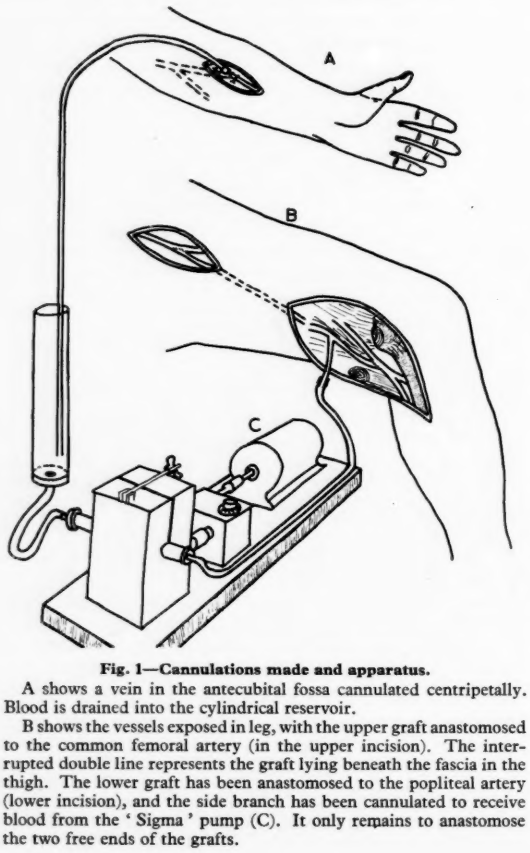

Fig. 1—Cannulations made and apparatus.

A shows a vein in the antecubital fossa cannulated centripetally. Blood is drained into the cylindrical reservoir.

B shows the vessels exposed in leg, with the upper graft anastomosed to the common femoral artery (in the upper incision). The interrupted double line represents the graft lying beneath the fascia in the thigh. The lower graft has been anastomosed to the popliteal artery (lower incision), and the side branch has been cannulated to receive blood from the 'Sigma' pump (C). It only remains to anastomose the two free ends of the grafts.

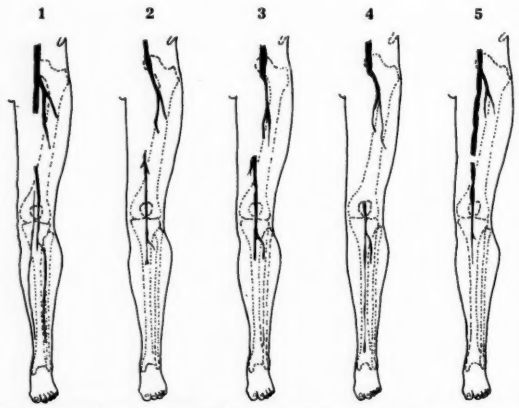

Fig. 2—Result of arteriography and extent of disease in cases 1–5 whose legs were perfused.

The disease in cases 1 and 5 was on the right side, but for the purpose of comparison it is shown as if it were in the left leg. X-rays of the lower leg and ankle were not taken in cases 2 and 3. The distal vessels are most severely affected in case 5. See table II.

Trial

It was thought that if the circulation through the smaller distal vessels of the limb could be maintained artificially while the main artery was occluded during the insertion of the graft, the chances of a successful outcome might be greater.

With perfusion, restorative operations might be extended to cases shown on arteriography to have such severe peripheral disease, which otherwise would be classed as unsuitable.

Methods

Principle

An intravenous dose of heparin is given to prevent clotting. A vein in the antecubital fossa is cannulated, and from this venous blood is conducted into a reservoir (fig. 1). Blood is pumped from here into the artery below the occlusion. The venous blood used for perfusion is about 60% saturated with oxygen, but the saturation may be increased by heating the limb. Copious bleeding is ensured by a sphygmomanometer cuff placed around the arm, inflated to 60 mm. Hg. Venous return from the perfused limb is via the natural channel—the leg veins.

Apparatus

The venous cannula is flexible, consisting of a rigid nylon tube which is inserted into the vein, connected to a solid turned nylon adaptor by a flexible, clear polyvinyl-chloride (P.V.C.) tube (Drew et al. 1957). The diameter may be 4–6 mm. The adaptor is inserted into a $^1/_4$ in. (6·0 mm.) internal-diameter P.V.C. hose which leads to a reservoir. The reservoir is a cylinder of rigid P.V.C. and is of $1^1/_2$ in. (37·0 mm.) internal diameter.

TABLE II—CLINICAL FEATURES, OPERATION DETAILS, AND RESULTS OF PERFUSION IN 6 CASES OF ARTERY-GRAFTING

Case no.	Age (yr.)	Extent of disease (arteriography, fig. 2)	Pulses (preop.)				Operation	Perfusion			Pulses (postop.)				Remarks	Result
			F.	Pop.	P.T.	D.P.		Duration (min.)	Rate (ml. per min.)	Site	F.	Pop.	P.T.	D.P.		
1	52	Rest pain. Claudication at 100 yd. Femoral artery blocked. Severe disease of anterior and posterior tibial vessels	±	−	−	−	Bypass graft, common femoral to popliteal; graft 38 cm. long	90	80–120	Lower graft	+	+	+	+	Breakdown of perfusion caused longer perfusion-time	Satisfactory
2	57	Intermittent claudication at 50 yd. Occlusion of femoral artery	+	−	−	−	Bypass graft, common femoral to popliteal; graft 38 cm. long	? 100	90	Lower graft	+	+	+	+	Has graft functioning on other leg	,,
3	51	Gangrene of great toe. Rest pain and claudication. Femoral artery occluded	+	−	−	−	Bypass graft, common femoral to popliteal; graft 44 cm. long	60	270	Lower graft	+	+	+	+	Previously unhealed great toe amputation healing	,,
4	60	Wet gangrene of 4th and 5th toes. Severe rest pain. Femoral and popliteal arteries blocked. Patent but severely diseased posterior tibial artery	+	−	−	−	Bypass graft, common femoral to popliteal; graft 40 cm. long	50	50	Lower graft	+	+	+	+	Amputation 4th and 5th toes	,,
5	47	Anæsthesia of toes. Severe rest pain. Block 1 cm. long of mid-femoral artery but severe disease of anterior and posterior tibial arteries	+	−	−	−	Bypass graft, common femoral to popliteal; graft 35 cm. long	40	150	Lower graft	+	+	−	−	—	,,
6	69	Ruptured aneurysm common and external iliac arteries	+	+	+	+	Bypass graft, common iliac to external iliac, exclusion of aneurysm; graft 15 cm long	60	60	Inf. epigastric artery	+	+	+	+	—	,,

F. = femoral. Pop. = popliteal. P.T. = posterior tibial. D.P. = dorsalis pedis.
The return of pulses after operation is sometimes delayed for several days. Absent distal pulses are quite compatible with relief of symptoms (case 5).

From the bottom of the reservoir a $^1/_4$ in. (6·0 mm.) P.V.C. hose leads to a Sigma or deBakey type pump, and a similar hose connects the pump to the arterial cannula which, like the venous one, is flexible.

Technique of Bypass Grafting from Common Femoral to Popliteal Artery

The clotting-time of the blood is estimated by the method of Dale and Laidlaw (1911). The anæsthetised patient lies supine on the operating-table with diseased leg abducted and externally rotated at the hip and flexed at the knee. The popliteal artery is approached through an incision on the medial aspect of the leg. The insertion of gracilis, sartorius, and semitendinosus is divided. The medial head of the gastrocnemius, and if necessary that part of the soleus origin which is attached to the soleal line on the tibia, are divided and displaced backwards.

The patent vessel below the block is incised, and any atheromatous deposits are removed until a free " bleed-back " from the distal end of the artery is observed.

The assistant meanwhile reconstitutes two freeze-dried homografts of such combined length as to span the distance from the common femoral to the popliteal artery. Each consists of the common, external iliac, and upper femoral arteries. All the side branches are tied off or sutured except the internal iliac branch, which is left about 1 in. (2·5 cm.) long. The surgeon then anastomoses the end of one of the grafts to the opening in the popliteal artery. While this anastomosis is being made, the patient is heparinised with heparin 1 mg. per kg. body-weight. The assistant cannulates the basilic or median cubital vein centripetally. The apparatus is charged with blood from the patient until the arterial cannula is filled, and the arterial cannula is inserted into the internal iliac branch of the graft and tied in. The free end of the graft is temporarily closed by a bulldog clip and the perfusion started. The surgeon is now free to continue the operation secure in the knowledge that the patency of the lower graft, the leg vessels, and the anastomosis between them is assured by a stream of heparinised blood.

A separate vertical incision in the groin exposes the common femoral artery and its two terminal branches—the profunda and superficial femoral arteries. If necessary, the external iliac artery can be exposed through an additional wound. The common femoral artery is clamped, and the natural blood-supply to the limb is now cut off except for that entering it by the cruciate anastomosis via the buttock; and until the completion of the operation the nutrition of and the blood-flow in the limb depend almost entirely on perfused blood. This period may be as long as an hour according to circumstances. Without perfusion the limb would be almost totally ischæmic during this time.

An incision is made in the common femoral artery, and here again extensive atheromatous deposits may need to be removed. An end of the second graft is anastomosed to this incision, taking as much time as is necessary to ensure a perfect suture line. The lower end of the upper graft is passed down the thigh under the fascia to emerge in the lower wound. Redundant graft is excised, and the two free ends of the grafts are joined (fig. 1). The perfusion is stopped. The arterial cannula is removed from the side branch of the lower graft, which is temporarily clamped. The bulldog clip on the upper end of the lower graft is released and reapplied just below the side branch. The main vessel is momentarily released, and a jet of blood washes out any clot in the upper graft. The side branch is tied off and the bulldog clip removed. Finally the upper clamp is taken away, thus re-establishing the circulation. The wound is closed by replacing muscle origins and suturing the deep fascia with catgut. No drains are used. The clotting-time is measured and sufficient protamine sulphate given to restore it to normal.

Results

The perfusion technique has been used on six patients. The arteriograms of five of them (fig. 2) show the extent of the disease. Case 6, with a dissecting aneurysm of the common iliac artery, did not undergo arteriography since clinical examination sufficed.

Table II expresses briefly the clinical condition of the patients before and after the operation and gives some of the operation and perfusion details. There were no failures.

Conclusion

While this study covers only a few cases, the results are encouraging. The perfusion technique interferes in no way with the operation and does not seem to have any disadvantages. The risk of hæmorrhage is not increased; no difficulty has been experienced in securing a sound anastomosis; and hæmorrhage from the wound during the operation has not been troublesome. At the end of the operation the clotting-time is restored to normal with protamine; no further anticoagulants are used, and in no case has postoperative hæmorrhage occurred.

In table I one other patient is shown to have had a graft inserted. He had a duodenal ulcer and was not perfused because of the supposed risk of hæmorrhage from his ulcer under the influence of heparin (Rains et al. 1957). His graft thrombosed and ultimately he lost his limb.

In the future a similar perfusion method can be adapted to maintain the vitality of both limbs in cases of aortic aneurysm. Further, this method has an application in the treatment of the acutely ischæmic limb before restoring the circulation by washing out the products of tissue ischæmia. Thompson and Campbell (1959) have shown experimentally how this may be possible. The perfusate of dextran taken from the femoral vein is discarded and any tendency towards the " crush syndrome " (acute renal failure) averted (*Lancet* 1959).

It is also possible that an isolated neoplasm of a limb or organ could be effectively treated by perfusion of alkylating agents (Creech et al. 1958).

We would like to thank the members of the heart-lung team—Prof. A. L. d'Abreu, Mr. L. D. Abrams, Mr. J. Fejfar, and Mr. R. Lightwood—for their help.

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THYROID ACROPACHY

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THYROID acropachy is one of the more odd manifestations of endocrine disorder, and how or why it arises is not at all clear. The changes consist in clubbing of the fingers and toes, periosteal new bone formation involving the phalanges and other distal long bones, and swelling of the soft tissues of the extremities, especially those overlying the affected bones (figs. 1 and 2). These changes are nearly always associated with past or present hyperthyroidism, exophthalmos, and pretibial myxœdema. The disorder seems to be rare, judging by the few reported cases; but this apparent evidence of rarity is probably misleading because the condition is often rather inconspicuous and usually causes no symptoms or disability.

I describe here six cases and compare the findings with those in thirteen others previously reported (see table).

Case-reports

Case 1.—Man, aged 61. Hyperthyroidism with exophthalmos began in 1949; thyroidectomy was done the following year. He was well for a year; but in 1951 pretibial myxœdema began to develop, and this grew steadily worse as did his exophthalmos. He also became hypothyroid and has required thyroid gr. 2 daily since 1952. Various treatments were tried for the pretibial myxœdema without effect; this and the exophthalmos have not changed since 1952. Early in 1955 he noticed painless swelling in both hands; the swelling increased for a few months and has remained unchanged since.

Fig. 1—Case 1: X-ray showing characteristic new-bone formation in acropachy, most pronounced on extensor surface of first metacarpal.

The changes of acropachy was more pronounced than in the other five cases. The fingers and toes were clubbed. Periosteal bone changes (fig. 1) were present in the metacarpals, metatarsals, phalanges, and distal ends of the radius, ulna, tibia, and fibula. There was considerable swelling of the soft tissues overlying the affected bones (fig. 2). The joints were unaffected, and there was no muscular wasting; the affected parts were painless and not hot. Apart from exophthalmos there was no change in the tissues of the face. The serum calcium was 7·9 mg. per 100 ml., phosphorus 5·0 mg. per 100 ml., alkaline phosphatase 5·5 King-Armstrong (K.A.) units. Erythrocyte-sedimentation rate (E.S.R.) 16 mm. in the first hour (Westergren). Skull X-ray normal.

Case 2.—Woman, aged 49. Hyperthyroidism and exophthalmos began in 1955 and thyroidectomy was done in April, 1956. Three months later hypothyroidism became evident and thyroid was started, gr. 1 (later gr. 3) daily; this has been continued up to the present time. Pretibial myxœdema began to appear within a month of operation and steadily increased; exophthalmos also progressed. In January, 1958, prednisone was given on account of increasing exophthalmos; this produced a temporary decrease in both exophthalmos and pretibial myxœdema, but after about three weeks, while high dosage was continued, both relapsed and became worse than ever. Orbital decompressions were performed by Mr. Harvey Jackson in March and April, 1958, with very good results. Changes of thyroid acropachy were first noticed in June, 1958, and have become more pronounced since.

Fig. 2—Case 1: clubbing and soft-tissue swelling, particularly over first two metacarpals.

The fingers and toes were clubbed. There was pronounced soft-tissue swelling of the hands, less localised to the parts overlying affected bones than in case 1. Periosteal new-bone formation was present in the metacarpals and phalanges, but the X-ray changes were slight compared with those in case 1.

FINDINGS IN 19 CASES OF ACROPACHY

Case	Age (yr.) at onset of acropachy	Sex	Pretibial myxœdema	Exophthalmos	Past or present hyperthyroidism	Thyroid state at onset of acropachy	Time from onset of hyperthyroidism to acropachy (yr.)	Clubbing	Soft-tissue swelling	Radiological change
Present series:										
Case 1	61	M	+	+	+	Hypo-	6	+	+	+
Case 2	47	F	+	+	+	Hypo-	3	+	+	+
Case 3	51	F	+	+	+	Eu-	12	+	+	−
Case 4	57	F	+	+	+	Eu-	8	−	+	+
Case 5	62	F	+	+	+	Hypo-	?13	+	+	+
Case 6	38	F	+	+	+	Hyper-	10	+	+	+
Reported cases:										
Thomas (1933)	22	M	+	+	+	Hypo-	3	+	+	+
Cushing (1937)	37	M	+	+	+	Hypo-	8	+	+	+
Rynearson and Sarcasa (1941)	43	M	+	+	+	Hypo-	6/52	+	−	+
Greene (1951) 1	73	M	+	+	+	Eu-	10	+	+	+
,, ,, 2	?	M	−	+	−	Eu-	?	+	±	−
Levitt (1953)	?	M	+	+	+	?	?	+	+	+
Engel (1953)	41	F	+	+	+	Hypo-	2	+	+	+
Inch and Rolland (1953) 1	38	F	+	+	+	Hypo-	"soon"	+	−	+
,, ,, 2	36	M	+	+	+	Eu-	16	+	±	+
McGill (1957)	51	M	+	+	+	Eu-	3	+	±	+
Freeman (1958) 1	56	M	−	+	+	Hypo-	28	+	−	−
,, 2	54	M	−	+	+	Hyper-	3/12	+	−	−
Diamond (1959)	24	M	+	+	+	Eu-	4	−	+	+

Some stiffness and discomfort in the hands developed after the acropachy appeared; there was no evidence of arthritis or muscular wasting, but there was some loss of power in grip. In the face there was no change other than residual effects of "mooning" from prednisone. The serum calcium was 10·6 mg. per 100 ml., phosphorus 3·6 mg. per 100 ml., alkaline-phosphatase 9 K.A. units. E.S.R. 10 mm. in the first hour. ^{131}I uptake by the thyroid was very low and was unaffected by thyroid-stimulating hormone given in two doses each of 10 units after three weeks without thyroid treatment. Forearm blood-flow estimated by venous occlusion plethysmography was found to be normal. The urinary œstrogen excretion was within normal limits. Skull X-ray was normal. Precipitin and agglutination tests on the patient's serum with thyroid antigen were negative.

Case 3.—Woman, aged 51. Thyroidectomy was done in 1946 on account of hyperthyroidism with exophthalmos. Soon after operation pretibial myxœdema began to appear and increased steadily despite many attempts at treatment; finally it became very severe and extensive. Since 1954 it has changed little. Exophthalmos also increased for several years after thyroidectomy and some ophthalmoplegia developed; later both regressed a little. The patient has been euthyroid since thyroidectomy.

The hands were inspected from time to time for changes of acropachy. There was nothing abnormal until July, 1958, when clubbing of the fingers was noted. There was also some soft-tissue swelling of the hands, but no periosteal new-bone formation was detected in X-rays of the hands. The serum calcium was 9·1 mg. per 100 ml., phosphorus 4·9 mg. per 100 ml., E.S.R. 20 mm. in the first hour.

Case 4.—Woman, aged 58. Thyrotoxicosis without eye signs developed in 1950. Thyroidectomy was done in 1951, and soon afterwards exophthalmos and pretibial myxœdema developed. The exophthalmos never became severe; the pretibial myxœdema advanced slowly with fluctuations but has never become extensive. In 1957 thyrotoxicosis recurred and was treated with radio-iodine; there was no change in exophthalmos and slight increase in pretibial myxœdema. Changes of thyroid acropachy were first noticed in 1958.

There was no clubbing of the fingers, but there was periosteal new-bone formation and overlying soft-tissue swelling which involved the first metacarpal obviously and was possibly present elsewhere in the hands. The condition was symptomless. The localisation of the changes of acropachy in this patient are notable; the absence of clubbing is unusual but has been described before (Diamond 1959). Otherwise the changes were quite typical. Serum calcium 10·4 mg. per 100 ml., phosphorus 3·9 mg. per 100 ml., alkaline-phosphatase 6 K.A. units, E.S.R. 7 mm. in the first hour.

Case 5.—Woman, aged 62. Hyperthyroidism developed in 1944 and was treated by thyroidectomy; subsequently the patient became hypothyroid and has taken gr. 2 of thyroid daily since. Moderate exophthalmos developed soon after operation and has been unchanged since. Pretibial myxœdema began to appear on the left leg eight months after operation, became bilateral, and has gradually progressed and become severe. The patient noticed swelling over the second left metacarpal after minor trauma in 1957. When acropachy was first present is uncertain; it causes no symptoms. The fingers are clubbed, and periosteal new-bone formation and soft-tissue swelling, notably patchy in distribution, involve the metacarpals and phalanges. Precipitin and agglutination tests on the patient's serum with thyroid antigen were negative.

Case 6.—Woman, aged 36. Hyperthyroidism developed in 1955 and was treated by thyroidectomy. Moderate exophthalmos was present before thyroidectomy and has not greatly changed since. Pretibial myxœdema appeared a few months after thyroidectomy and became moderately severe. Hyperthyroidism recurred in 1959 and was treated with radioactive iodine. It was noted then that the fingers were clubbed and the soft tissues of the hands thickened. There was very slight periosteal new-bone formation.

Discussion

Acropachy is the last and rarest part of a syndrome, the other parts being hyperthyroidism, exophthalmos, and pretibial myxœdema, usually arising in that order. The changes have been thought to be due to a disorder of hormone secretion by the anterior pituitary, and in two patients with acropachy eosinophil hyperplasia or adenoma has been described (Freeman 1958). In the present series skull X-rays showed normal pituitary fossæ. Possibly autoimmunisation plays a part, but so far there has been no positive evidence. The great majority of described cases of acropachy have been in males.

Why the syndrome of Graves' disease with pretibial myxœdema and acropachy should develop piecemeal over a variable and often long period is obscure. In the cases described here and in other reports, the changes of acropachy have invariably been found in association with other features of the syndrome, usually all of them, and acropachy has not been described as occurring alone or in any other condition. Acropachy usually appears some time after the other components of the syndrome, when hyperthyroidism has been treated, and it is therefore rarely present with active hyperthyroidism as in case 6 and in a case reported by Freeman (1958). The interval

between the onset of hyperthyroidism and the recognition of acropachy varied from a few weeks to twenty-eight years (see table). Hyperthyroidism has been recognised at some stage in all patients with acropachy except one (Greene 1951); exophthalmos has been present in all, and pretibial myxœdema in the majority.

The changes in thyroid acropachy seem to be unique, and the question of differential diagnosis hardly arises. In some of the earlier described cases there was confusion with hypertrophic pulmonary osteoarthropathy. In acropachy the periosteal bone changes are quite different in appearance: they simulate bubbles on the bone surface, and they are differently situated, being on more peripheral parts of the skeleton. Also the characteristic heat, pain, and evidence of increased bone blood-flow (Ginsberg 1958) in pulmonary osteoarthropathy is absent in acropachy. The soft-tissue thickening of acropachy is an important diagnostic feature, particularly when localised over the affected bones. In acromegaly, occasionally associated with hyperthyroidism, the changes in the hands and elsewhere should not be confused with those of acropachy, although some new bone formation occurs. There is a rare familial condition—idiopathic osteodystrophy or pachydermoperiostosis (Angel 1957) in which clubbing and thickening of the tissues of the hands, feet, and face develop early in adult life. This condition has some resemblance to acropachy, but it is not associated with other features of the acropachy syndrome.

Symptoms from thyroid acropachy are unusual, and treatment is therefore not an important problem. There may be complaint of stiffness due to generalised soft-tissue swelling of the hands; but the joints do not seem to be involved, and there is no evidence of muscular weakness or wasting. The natural course of thyroid acropachy is uncertain; in some patients there has been no change for several years; possibly, as with other features of Graves' disease, partial or complete remission may occur naturally after a time.

The frequency of thyroid acropachy is very difficult to determine since it may appear so many years after the onset of thyrotoxicosis that an ordinary follow-up would be inadequate. The present series of six cases were met with over a period of four years during which there were about five hundred new cases of hyperthyroidism. Possibly acropachy eventually develops in about 1% of patients with hyperthyroidism.

Thyroid acropachy must be added to the long list of miscellaneous conditions associated with clubbing, and the changes in acropachy are not readily explained by any of the mechanisms or causes of clubbing which have been suggested in certain other disorders.

Summary

Six cases of thyroid acropachy are described. Acropachy consists of clubbing of fingers and toes, distal periosteal bone change, and swelling of the overlying soft tissues.

The condition arises occasionally as a final phase of development of the acropachy syndrome of hyperthyroidism, exophthalmos, and pretibial myxœdema.

The cause of acropachy is obscure; but apparently in some circumstances certain of the peripheral tissues undergo peculiar changes, possibly under the influence of a pituitary hormone.

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References at foot of next column

PREGNANCY AFTER TUBERCULOSIS OF THE FALLOPIAN TUBES

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Rabau first reported a pregnancy after the successful treatment of proved endometrial tuberculosis in 1952, and several other cases have been described since. We have been unable to find any reference to proved tubal tuberculosis followed by pregnancy, although in one of Earn's (1958) cases of endometrial tuberculosis the left fallopian tube was palpable at the first examination. We therefore present the following case-report, which shows that pregnancy is possible after tuberculosis of the fallopian tubes has been treated medically.

Case-report

The patient, aged 25, who had been married 9 months, was referred, on June 29, 1955, to S. W. L. with suspected extra-uterine pregnancy. Her last normal menstrual period was at the end of April—i.e., 8–9 weeks previously. From the last week in May until the time of examination she had had irregular vaginal bleeding, and had passed occasional small clots. She also had cramp-like lower abdominal pain. She denied any previous serious illness or familial tuberculosis, although 2 weeks later her mother underwent nephrectomy for renal tuberculosis.

Examination

She seemed to be healthy and was of medium build. Her heart and lungs were normal, and the temperature and pulse-rate were not increased. The abdomen moved easily on respiration; no tumour was felt but there was slight tenderness on both sides of the lower abdomen. Bimanual examination revealed a slightly enlarged uterus and an irregular, slightly tender mass, which appeared to be fixed to the uterus, in the pouch of Douglas.

The patient was admitted to a nursing home for observation because the diagnosis was in doubt. On June 30 her condition was unchanged, but next evening she had fairly severe abdominal pain. She was not in a state of shock and she had no signs of intra-abdominal bleeding. Because the mass in the pouch of Douglas was more tender, an examination under anæsthesia and possibly laparotomy was planned for next morning.

Operation and Course

Under general anæsthesia (July 2) the previous findings in the pelvis were confirmed. As an ectopic pregnancy could not be excluded, laparotomy was performed through a midline sub-umbilical incision. The omentum was adhering to the uterine fundus and covering the pelvis. When this was freed the uterus was found to be enlarged to the size of a 6–8 weeks pregnancy by multiple small fibroids. The mass in the pouch of Douglas comprised the swollen and inflamed fallopian tubes. The left tube was distended to at least 1 in. diameter, and the right to about $^1/_2$ in.; thin yellow pus was escaping from their fimbrial

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ends, from which a swab was taken for examination. The abdomen was closed without drainage, and the patient returned to the ward in good condition.

Direct microscopical examination (J. A. L. J.) showed pus-cell debris and necrotic material with some intact leucocytes and lymphocytes, and a few giant cells. No gram-positive organisms or acid-fast bacilli were seen, but a tuberculous infection was suspected. Culture of the pus for these organisms was arranged.

By the 3rd postoperative day the patient had a temperature of 102°F, with a corresponding tachycardia. That evening she had a hæmoptysis, and was examined by J. A. L. J. The heart sounds and rhythm were normal, and the blood-pressure was 120/80 mm. Hg. The patient said she had had a pain in the left axilla at the level of the 6th or 7th rib, some 36–48 hours before the hæmoptysis. A slight friction rub and a few crepitations were heard in the left submammary area. The respiratory rate was increased, but deep breathing did not cause pain. Sputum (3 specimens) was negative for tubercule bacilli.

A small pulmonary embolus was diagnosed provisionally, but in view of the abdominal findings the possibility of pulmonary tuberculosis was considered, and treatment with streptomycin and isoniazid was instituted. The pyrexia and tachycardia disappeared in 3 weeks, and chest radiographs on July 18 showed a very small effusion within the left pleural cavity, but the rest of the lung fields were clear. A further radiograph on Aug. 3 showed that the left costophrenic sinus was clear, although increased density in this area persisted. Convalescence was uneventful, and the patient was allowed home in mid-August, her medical treatment being continued.

When reviewed on Sept. 10, the patient's general condition had improved, although pyrexia (99·6–100·4°F) had returned, with some sweating. Her weight had increased by 4½ lb. Radiographs showed no active lesion in the lungs, but a large calcified abdominal gland was noticed. The hypogastrium was tender.

The results of the bacterial cultures became available. Blood-agar plates were sterile after 4 days' incubation, but after 7 weeks on Lowenstein and Jensen medium typical colonies of tubercle bacilli were present. Acid-fast and alcohol-fast tubercle bacilli were seen microscopically. Examination of the blood showed hæmoglobin (Hb) 90%; red blood-cells 4,000,000 per c.mm.; white blood-cells 11,000 per c.mm.; hæmatocrit 35%; erythrocyte-sedimentation rate (E.S.R.) 10 mm. in the 1st hour (Westergren). Streptomycin therapy was replaced by *p*-aminosalicylic acid, and isoniazid was continued.

On Oct. 12 the patient's temperature was lower and her weight had increased. By Nov. 1 her temperature was normal apart from an occasional spike, and the E.S.R. had fallen to 7 mm. in the 1st hour. Her condition remained unchanged for several weeks, but by Dec. 28 a definite pattern of pyrexia was apparent during the progestational phase of the menstrual cycle. Her weight had increased further but the E.S.R. had risen slightly to 11 mm. in the 1st hour, and the hæmatocrit had fallen to 36%.

Menstruation had returned in September, without pain or intermenstrual bleeding. On Jan. 30, 1956, no abnormality was detected in the abdomen, and on vaginal examination the uterus seemed normal. The right fallopian tube could not be felt, but the left was still much enlarged and thickened.

On Feb. 3 the E.S.R. was 18 mm. in the 1st hour, Hb 84%, and hæmatocrit 36%. No lung lesion was found clinically or radiographically. The patient was readmitted to the nursing home for complete rest, and further streptomycin was given. By March 9 her condition had improved considerably, and she was allowed to go home. She still had pyrexia in the progestational phase of the menstrual cycle, but it now never rose above 99°F. The E.S.R. was 11 mm. in the 1st hour, Hb 88%, and hæmatocrit 36%; her weight had increased to 11 st. 10 lb.

First Pregnancy

The improvement continued, but on May 23 she complained of some dizziness, and although no 8th nerve lesion was detected streptomycin was discontinued as a precautionary measure. On June 6 menstruation was 14 days overdue, and pregnancy was confirmed by a positive Hogben test in mid-July. By the end of July, because she was much troubled by vomiting, the *p*-aminosalicylic acid was replaced by streptomycin. On Aug. 3 she aborted incompletely a ten-week fœtus. Next day, at curettage under general anæsthesia, several fibroids were palpated. Convalescence was complicated by a thrombophlebitis of the right internal saphenous vein. Menstruation returned on Sept. 9. On Sept. 29 the E.S.R. was 10 mm. in the 1st hour.

At postoperative review on Oct. 4 the right leg showed no sign of the previous thrombosis. The cervix was healthy, and the uterus and fibroids were well involuted. She had slight dysuria, but no cause was found.

At the end of October dizziness and tinnitus had returned, but the E.S.R. was 8 mm. in the 1st hour, and her general condition was good. Streptomycin was stopped, and all other treatment was scaled down. She was not seen again until March 8, 1957, when she had had no treatment for about 2 months. She was well, her weight had increased, and the E.S.R. was 3 mm. in the 1st hour.

Second Pregnancy

At the end of May she again reported that menstruation was overdue (last menstrual period April 16) and a Hogben test confirmed pregnancy. In view of the previous miscarriage 6 (25 mg.) pellets of progesterone were implanted deep to the fascia lata. She was again given *p*-aminosalicylic acid.

Pregnancy proceeded normally (blood-pressure 120/80 mm. Hg; no albuminuria) until Sept. 9, when decalcification of her teeth was noted. She was given calcium and vitamin D, and for the next 2 months she seemed to be normal.

Just before Christmas her right leg had been swollen for 5 days but had improved since. On Jan. 3, 1958, slight œdema was found, but no evidence of any clot formation. The blood-pressure was 130/80, a trace of albuminuria was found, and the fœtal heart was heard. The fœtal head had not engaged in the pelvic brim. The patient was advised to rest.

On Jan. 10 the blood-pressure had risen to 150/90 and the urine still contained a slight trace of albumin. The fœtus was presenting by the vertex, and the fœtal heart was heard. The patient was advised to continue resting at home. She was admitted to the nursing home on Jan. 17 as she feared she might be isolated at her home in the country by a snow storm. With complete rest in bed the blood-pressure fell to 140/90 and the urine became albumin-free.

Labour started spontaneously on Jan. 28—i.e., 285 days after the first day of her last menstrual period. Progress was very slow, with weak irregular pains; after 36 hours the cervix was only three-fingers dilated, and the head was still free. In view of the length of labour, the uterine inertia, and the non-engagement of the head, a lower-uterine-segment cæsarean section was performed on Jan. 29, and a live female infant weighing 10 lb. was delivered. At operation cephalopelvic disproportion was noted, and the fibroids were still present, but both fallopian tubes looked normal, without evidence of previous disease. There was a large placental infarct, and the liquor was heavily stained with meconium.

Convalescence was uneventful at first. Careful and regular examinations showed no evidence of venous thrombosis. The patient got up daily from the 3rd day, and moved about her room. On the 10th postoperative day, while she was cleaning her teeth in the bathroom, she collapsed from a pulmonary embolus, and despite morphine and intravenous heparin she died 20 minutes later. The infant has progressed satisfactorily.

Discussion

Despite this patient's unfortunate death her history shows that in cases of tuberculous salpingitis the radical and surgical treatment previously practised by Stallworthy (1952) and others may no longer always be necessary, and that with present-day medical treatment even considerable damage to the fallopian tubes by tuberculous disease does not always mean sterility.

This case was treated along the lines recommended by Hallum and Thomas (1955) and Norburn and Walker (1956) with the addition of isoniaziad 100–150 mg. daily. As in Rabau's case, the first pregnancy after treatment ended in early abortion. We do not think the post-operative thrombophlebitis was necessarily associated with the tuberculous infection.

Summary

A patient with tuberculosis of the fallopian tubes, treated medically, had afterwards two pregnancies which resulted in an abortion and a healthy infant.

At the time of the cæsarean section both fallopian tubes were free from macroscopic signs of inflammation.

Three consecutive operations were followed by venous thrombophlebitis. The third proved fatal because of pulmonary embolism.

We wish to thank Dr. D. S. Wilson and Lieut.-Colonel D. G. C. Whyte, D.S.O., for their assistance with the anæsthesia and radiology; and Miss E. Scott, S.R.N., S.C.M., and her staff for nursing the patient.

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STERNAL TRACTION FOR THE FLAIL CHEST

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SINCE Jones and Richardson (1926) first described a method of controlling paradoxical respiration after chest trauma by skeletal traction on the sternum, using a gynæcological "bullet forceps", several reports have suggested other methods and instruments found valuable.

Butler (1938) and Williams (1948) advocated the use of towel-clips to grasp the ribs; Jaslow (1946) used coat-hanger hooks screwed into the sternum. All three workers employed weight traction.

Proctor and London (1955) used "cup hooks" in the sternum fixed to a special bed frame, while Heroy and Eggle-stone (1951) made drill holes in the sternum and applied a clamp and 10 lb. traction. Ritter and Kaye (1944) used perichondral wires with weight traction. Other workers have advocated open reduction of sternal fractures and fixation with plates (Hendry 1957) or crossed Kirschner wires (McKim 1943), and finally Coleman and Coleman (1950) suggested open reduction of the multiple rib fractures and fixation with wire sutures. Birchfield and Grant (1956) also recommended this method of managing the "stove-in" chest.

Recently for sternal fixation in a patient with multiple injuries I used an instrument available in most traumatic centres—i.e., a skull calliper—and found it to be both easy to apply and effective.

Case-report

A man, aged 27, was involved in an accident at work in a textile factory on Jan. 6, 1959, when his right hand was trapped in a machine. His arms, head, and trunk were drawn between the rollers, crushing him and at the same time enveloping him in several layers of fabric. The machine had to be reversed to roll him out and he was removed from the wrappings unconscious, deeply cyanosed, and not breathing. After artificial respiration by a workmate he regained consciousness. On arrival in hospital, about half an hour after the accident, he was conscious but grossly shocked. His pulse and blood-pressure were unrecordable, and although there was no cyanosis there was severe respiratory distress. His injuries included compound fractures of the left humerus and left radius and ulna, a fracture of the ascending ramus of the mandible on the right, a fracture of the neck of the right scapula, fractures of the right radius and ulna, a subtrochanteric fracture of the right femur, and finally bilateral fractures of the second to ninth ribs inclusive in the anterior axillary lines (fig. 1). The entire anterior chest wall, an area measuring about 135 sq. in., was involved in paradoxical movement, and he showed the orbital hæmorrhages of traumatic asphyxia.

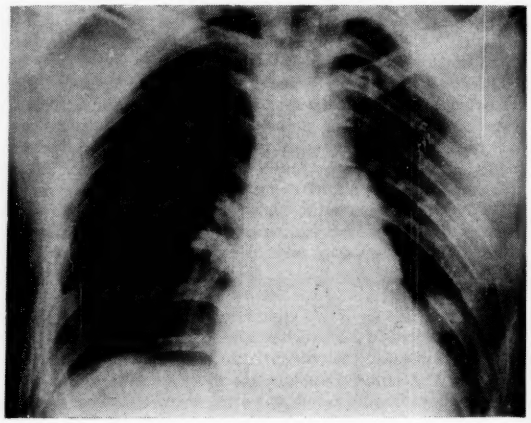

Fig. 1—Chest radiograph on the day after injury, showing multiple bilateral rib fractures.

After immediate splinting of the limb fractures, strapping the chest, and rapid infusion first of dextran and then of blood, his condition improved enough to allow operation, which was performed under general anæsthesia. First the chest wall was

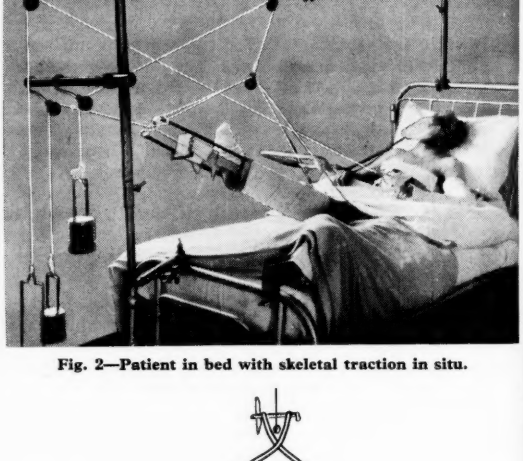

Fig. 2—Patient in bed with skeletal traction in situ.

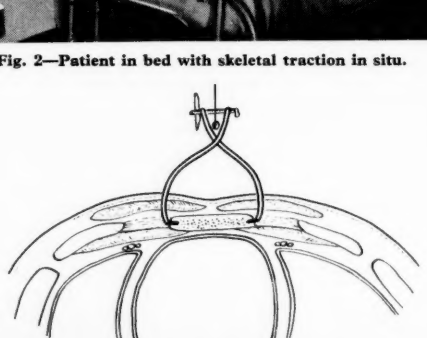

Fig. 3—Diagrammatic cross-section of anterior chest wall at the level of the 5th intercostal space.

enclosed in circumferential strapping, and then routine toilet and manipulation of the fractures was performed. The limb fractures were immobilised in plaster. After a total transfusion of 9 pints of blood his general condition was good, although, despite the strapping, there was still considerable paradoxical movement of the anterior chest wall.

For three days the improvement was maintained, and then a " wet-lung syndrome " supervened and the patient rapidly deteriorated. The respiratory rate rose to 60 per min. and the pulse-rate to 160 per min. The hæmoglobin fell from 92% on the morning after injury to 80%, and the white-blood-cell count rose to 25,600 per c.mm. Fixation of the flail chest segment was regarded as essential, and this was carried out as follows:

Under local anæsthesia, a transverse incision about 5 in. long was made across the sternum at the level of the sixth costal cartilage. The upper part of the rectus abdominis was divided, and the fifth intercostal space on each side was exposed by incising the anterior intercostal membrane. A Crutchfield skull calliper was used to grasp the sternum, the prongs biting into the lateral edges of the bone between the fifth and sixth cartilages on each side. The calliper was then tightened to gain a firm hold and traction of 14 lb. was applied over pulleys (figs. 2 and 3).

The patient's condition improved immediately and dramatically. The respiratory rate fell to 30 per min. and the pulse-rate to 110. The cyanosis cleared, the pain in the chest was relieved, and the patient was able to cough. But the paradoxical movement, though much reduced, was still present, and in fact could not be completely overcome even by pulling manually on the calliper with a much greater force. With this increased pull there was some discomfort from the calliper, but with 14 lb. there were no adverse symptoms. The wound was finally closed round the calliper.

Within twenty-four hours, the chest was clinically and radiographically dry, and thereafter the improvement was maintained. On Jan. 17, again under general anæsthesia, with the traction still in place, open reduction of the two forearm fractures was performed. Even at this time temporary removal of the traction was followed by rapid return of respiratory distress, but by mid-February there was radiographic early union of the rib fractures, and the traction was discontinued without return of paradoxical respiration. Since then progress has been uneventful. Apart from slight delay in the left forearm, the limb fractures have united satisfactorily; the patient's general condition is excellent; and there is no significant deformity of the chest wall.

Discussion

With the increasing number of road accidents, " stove-in " chests are being seen more commonly, and are usually the result of crushing by the steering-wheel during collision. The injury is frequently anterior and often involves the sternum as well as the ribs. Furthermore, frequently there are other injuries, sometimes very severe.

Although Hulman (1957) suggests that, in the management of such injuries, tracheotomy and bronchial aspiration are all that is required and gives physiological reasons for this, and Shefts (1956) states that " tracheotomy is almost mandatory ", there are disadvantages in this method—particularly the loss of the protective function of the upper air passages against infection. Many surgeons, therefore, prefer to avoid tracheotomy if possible. Open reduction of rib fractures, recommended in many centres, has the great disadvantage of converting a closed chest injury into an open one. Coleman and Coleman (1950) and Birchfield and Grant (1956) both confirm that the parietal pleura is always torn below the rib fractures, and recommend routine intercostal drainage after operation. Nevertheless the operation is a major one in a patient who may be in a grave state, as much from other injuries as from the thoracic lesion. Furthermore the operation requires expert thoracic surgical skill and nursing, neither of which may be available in the traumatic centre to which the patient is first admitted.

Other methods of skeletal traction have disadvantages. Towel clips placed round ribs or pericostal or perichondral wires may, as Shefts (1956) says, injure the internal mammary artery in their application, and " not infrequently the pleura or the lung may be involved ". Even if available, single screws in the sternum, cup hooks, and coat-hanger hooks are not mechanically sound. Clamps fixed to the sternum through drill holes involve the risk of the drill perforating the posterior sternal plate and injuring the mediastinum.

Moreover, with involvement of a large area of chest wall in the paradoxical movement, the forces required to stabilise the flail segment are relatively great. Although Cooper (1957) found $2^1/_2$ lb. traction effective, in this case not even 14 lb. was enough to control the flail segment completely. In normal quiet respiration the difference in negative pressure in the pleural cavity between inspiration and expiration is said to be 5 mm. Hg, or about $^1/_{10}$ lb. per sq. in. (Wright 1952). In flail chests, it is probably this decreasing negative pressure that causes the indrawing of the unstabilised segment of the thoracic cage on inspiration. In this patient, therefore, a theoretical traction force of $13^1/_2$ lb. should have controlled the anterior chest wall. Nevertheless even a much greater force did not completely prevent some indrawing. Presumably, therefore, the gross respiratory distress of a patient with a " stove-in " chest must result in an intrapleural pressure swing of much more than 5 mm. Hg, and thus the traction force required is consequently increased.

Thus very firm skeletal traction is required for adequate management of these cases. The skull calliper allows such firm traction to be applied, and furthermore is simple to apply, with little risk. The dissection required is not deep enough to involve the left pleural reflection, and the application of the clamp directly to the lateral edge of the sternum avoids the internal mammary artery which runs usually half an inch laterally. Its use is therefore advocated in the management of flail chests when the sternal segment of the chest wall is part of the unstable section.

Summary

In a man with severe multiple injuries a skull calliper was applied successfully to control paradoxical respiration in the flail chest. These allowed firm traction to be applied, and, although indrawing of the affected segment was not entirely prevented, the improvement in the patient's condition was dramatic and immediate.

I thank Dr. J. H. Dixon, but for whose skilful anæsthetics this treatment could not have been carried out; Mr. D. M. Dunn, who allowed me to treat this case in the early stages, for his help and encouragement in preparation of this paper; and Miss M. Fishwick for fig. 3, and the photographic department of the Royal National Orthopædic Hospital for fig. 1.

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THROMBOTIC THROMBOCYTOPENIC PURPURA

REMISSION ON TREATMENT WITH HEPARIN

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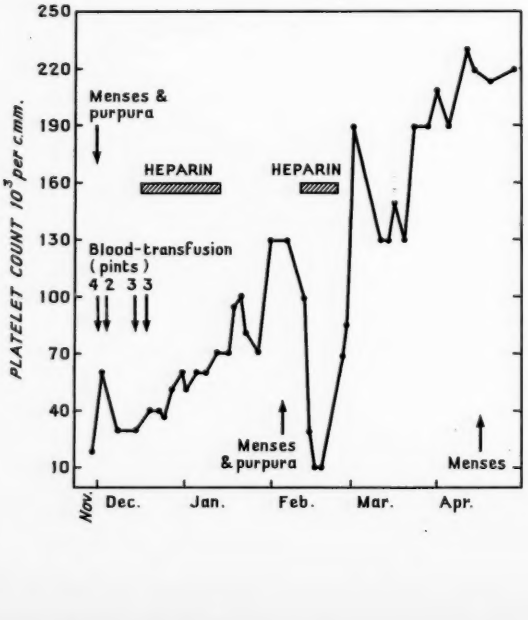
SINCE the original description of thrombotic thrombocytopenic purpura by Moschowitz (1924, 1925), about a hundred cases have been reported. Although in the clinical presentation considerable variation has been noted, there is a diagnostic syndrome of acute febrile hæmolytic anæmia, thrombocytopenia, and transient neurological signs present at some stage of the disease. The course is generally relentless and fatal. We report here a case in which heparin apparently induced two remissions.

Case-report

Mrs. A., aged 27, was admitted on Nov. 28, 1958, for an acute hæmorrhagic illness, with fever, severe anæmia, slight icterus and sore throat, and a raised erythrocyte-sedimentation rate. 9 days previously she had had an acute upper respiratory infection, followed 2 days later by a sore throat, generalised purpura of skin and mucous membranes, and vaginal bleeding. Sulphonamide and penicillin therapy had been given by her family doctor. 5 weeks before this a urinary-tract infection had been treated with sulphonamides.

Flexion in one knee was limited probably because of rheumatoid arthritis 4 years previously. (This had been associated with hyperglobulinæmia [total protein 8 g. per 100 ml. globulin 4 g.] and had been treated successfully with corticotrophin.) The liver, spleen, and superficial lymph-nodes were not palpable; the retinæ, nervous system, and mental state were normal; and there was no abnormality of the cardiorespiratory systems. Blood examination showed a hæmolytic anæmia with thrombocytopenia:

Hæmoglobin 37% (5·4 g. per 100 ml.). Packed-cell volume 17%. Mean corpuscular hæmoglobin concentration 32%. Anisocytosis and poikilocytosis; many spherocytes and fragmented red cells. Normoblasts 21 per 100 white cells; reticulocytes 21%; platelets 60,000 per c.mm.; white cells 16,900 per c.mm. (polymorphonuclears 69%, eosinophils 2%, lymphocytes 25%, metamyelocytes 4%). Many of the lymphocytes were early forms. Coombs' antiglobulin and platelet antibody tests negative. Several preparations for L.E. (lupus erythematosus) cells were negative and the serum proteins were normal. (Total protein 7 g. per 100 ml., albumin 4·5 g. per 100 ml., globulin 2·5 g. per 100 ml.)



Marrow from the iliac crest showed hyperplasia of the normoblast series and no abnormality of the white-cell series. Megakaryocytes were present in normal numbers but showed none of the cytoplasmic granularity usually associated with platelet production. Wassermann reaction was negative. A diagnosis of acquired hæmolytic anæmia with thrombocytopenia was made.

Progress

On the 2nd day in hospital the patient developed paræsthesiæ and weakness of the right arm and face with slurred speech, and the diagnosis was altered to thrombotic thrombocytopenic purpura. The hæmoglobin was now 22% (3·3 g. per 100 ml.) and the platelets 30,000 per c.mm. Prednisone, 40 mg. daily, was given for 2 days, and then increased to 60 mg. with the addition of 40 units of corticotrophin daily. 12 pints of blood, partly fresh, taken and administered through siliconed apparatus, was given to raise the low hæmoglobin and platelet levels. The hæmoglobin level repeatedly reached 60% but always fell to pretransfusion figures in about 2 days.

The general condition remained grave. Purpura and vaginal bleeding continued, and once or more daily there were neurological episodes, lasting 2-12 hours, with stupor, paresis, and behaviour and mental changes.

A feature of the blood-film at this stage was the daily variation in the number of spherocytes and fragmented red cells and the big variation in the number of primitive white cells.

On the 20th day heparin therapy was started, with a small dose of 1000 units intramuscularly every 4 hours. This did not increase coagulation-time, which was 7 minutes (Lee and White). After a day's heparin treatment there were no more neurological episodes, and by the 2nd day there was no fresh hæmorrhage, therefore the same dosage was continued. The hæmoglobin level and platelet-count rose steadily (see fig.) without further blood-transfusions. The white-cell count returned to normal levels although some primitive cells persisted; the reticulocytes fell and abnormal red cells disappeared.

Corticoid therapy was slowly discontinued and heparin therapy was stopped after 4 weeks. The patient was discharged ambulant and symptom-free with hæmoglobin 75% (10·9 g. per 100 ml.), and white cells 6200 per c.mm. (polymorph neutrophils 70%, eosinophils 4%, lymphocytes 25%, monocytes 1%). No abnormal red cells. Platelets 105,000 per c.mm. Reticulocytes 4%.

Second Episode

For 4 weeks she remained well. In the 5th week her usual menstrual loss started, but it was heavier than usual and accompanied by a sore throat and purpura of skin and mucous membranes. The hæmoglobin was 66% (9·1 g. per 100 ml.)—a drop of 9% in 3 days—and the platelet-count 130,000. She was readmitted and heparin therapy, without corticoids or blood-transfusion, was begun in the same dosage as before. Next day the platelets had fallen to 30,000, but there was neither new purpura nor excessive vaginal bleeding. Menstruation ceased 2 days later. Treatment was discontinued on the 12th day, and she was again discharged free of symptoms or signs. Since then, menstruation and dental extractions have been unaccompanied by excess blood loss or hæmatological changes.

Present Condition

The patient remains free from symptoms or abnormal signs. The most recent blood-count, 40 weeks after the completion of the second course of treatment, is: hæmoglobin 84% (12·1 g. per 100 ml.); white cells 6700 per c.mm. (differential count normal); platelets 160,000 per c.mm.

Discussion

In the first episode therapy was multiple but remission followed administration of heparin. In treating the relapse only heparin was used. The patient's recovery on this treatment is noteworthy because spontaneous remission in thrombotic thrombocytopenic purpura has not been reported, and death is usual within a month of the onset.

Delbeke and Coussement (1956) described the case of a child of 7 years who survived for 5 months. Thrombocytopenia but not anæmia remitted on steroid therapy. A relapse, uninfluenced by intensive therapy, followed 2 months after discontinuing treatment. The case of Engel et al. (1947) in which splenectomy was performed, remitted for 3 months but died in acute relapse.

We have found no examples of classical thrombotic thrombocytopenic purpura running a chronic course. Protracted cases appear to fall into three groups:

Rapid termination has been reported after long and varied illness which at first lacked the characteristics of the disease. (Laszlo et al. 1947, Fitzgerald et al. 1947, Biegelman 1951, Comess and Oyamada 1952).

The cases described by Brown and Norman (1946), Gendel et al. (1952), Fisher and Creed (1955), and Baez-Villasenor and Ambrosius (1957) appear to have been unclassifiable hæmatological disorders terminating in thrombotic thrombocytopenic purpura.

Gardner et al. (1951) and Meacham et al. (1951) recorded cases of acquired hæmolytic anæmias, responding to splenectomy, which in terminal illness showed the features of the syndrome.

We have been able to trace five non-fatal cases:

Shapiro et al. (1957) reported a 32-month survival after splenectomy and corticoid treatment: evidence of hæmolysis persisted. Siegel et al. (1954) reported a complete remission of similar duration, also following splenectomy and steroid therapy: L.E. cells were demonstrated 7 months after operation. Rodriguez et al. (1957) have reported complete remission for a year following splenectomy, and Burke and Hartmann (1959) complete remission in two cases following very large dosage of corticoids.

Treatment with blood-transfusion and corticoids is customary, and splenectomy has been performed on a number of occasions. Only in the cases cited above has therapy been of possible value.

In 1947, at a time when no case had been diagnosed during life, Singer et al. suggested the use of heparin. The suggestion was repeated, without clinical trial, by Singer et al. (1950) and Hauser et al. (1951). We have been able to find only two cases in which heparin was used. Adelson and Stefanini (1952) gave heparin sodium 75 mg. intravenously 4-hourly but abandoned the treatment after 2 days, and Adelson et al. (1954) apparently used the same dosage unsuccessfully for the same time in the terminal stage of a short illness. Hence the case we present is the first in which heparin seems to have induced a remission.

The mode of action of heparin, as an anticoagulant, is controversial. It prevents the agglutination and disintegration of platelets and may remove thrombin, thus interfering with the formation of fibrin. O'Brien (1958) suggested that it acts by combining with Christmas factor, thus lengthening the coagulation-time.

Despite the hazards inherent in giving heparin in the presence of hæmorrhage, its use in thrombotic thrombocytopenic purpura has a basis in the pathology of the condition.

Gore (1950) suggested that the primary defect is a subendothelial collection of hyaline material in the capillaries; this substance projects into the lumen and is covered by healthy endothelium. With excessive hyaline deposition, rupture takes place, platelets are withdrawn from the circulation by deposition on the roughened surface, and clotting follows. Using fluorescein-conjugated antibody, Craig and Gitlin (1957) identified the hyaline thrombi as a derivative of fibrinogen or fibrin. The view that the condition is primarily associated with damage to capillaries and arterioles is stressed by Meacham et al. (1951), Orbison (1952), and March (1954).

Further evidence of the secondary nature of the thrombocytopenia appears to be demonstrated in our case. We observed a marked fall in platelet-count only after clinical relapse with purpuric lesions and a fall in hæmoglobin level.

Symmers (1956) found the histological changes of thrombotic thrombocytopenic purpura before the symptoms had become manifest.

Hinstell and Kligerman (1959) have pointed out the high incidence of a hæmorrhagic diathesis in hyperglobulinæmias of various types. They suggest that some globulins may combine with clotting factors with resultant hæmorrhage. When such combinations dissociate, large amounts of clotting factors are released with consequent clot formation. These workers have demonstrated the combination of globulins with proaccelerin, accelerin, convertin, prothrombin and fibrinogen. This mechanism might play a part in the ætiology of thrombotic thrombocytopenic purpura in cases where hyperglobulinæmia is present.

Summary

In a case of thrombotic thrombocytopenic purpura clinical and hæmatological remission occurred on two occasions after the use of small doses of heparin.

We wish to thank Dr. J. B. Harman for his permission to publish this report and Mrs. M. Moore and the technicians of the hæmatological laboratory.

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". . . The relationship between Science and Art is similar in function to the very legs we stand and move on. These must be both independent of each other, and, at the same time, harmonious and simultaneous in synchronisation."—Mr. YEHUDI MENUHIN at a meeting of The Royal Institution of Great Britain on Jan. 30, 1959.

Preliminary Communications

HODGKIN'S DISEASE: A MATERNAL-TO-FŒTAL LYMPHOCYTE CHIMÆRA?

THE hypothesis we describe here is based on acquired tolerance, the probable ability of maternal leucocytes to reach the fœtal circulation, and the immunological theory of carcinogenesis.

Acquired tolerance is the "outcome of an induced central failure of the mechanism of immunological response brought about by the exposure of animals to antigenic stimuli before the maturation of the faculty of immunological response".[1] That this phenomenon exists has been amply demonstrated.[2]

If maternal leucocytes could enter the fœtal circulation by transplacental passage at a time when the fœtus is immunologically tolerant, then these leucocytes could persist and reproduce. The lymphocyte is most likely to do this because it has a long life-span [3 4] and can reproduce.[5–8] That maternal red blood-cells may reach the fœtus has been shown by several studies.[9 10] Since the small lymphocyte is of the same order of size as the red blood-cell it should also be able to pass the placental barrier. The mature fœtus (adult animal) could then be a lymphocyte chimæra. Maternal tumour cells, which are larger than red blood-cells, occasionally pass this barrier.[11]

In artificially produced lymphocyte chimæras, tolerance may be one-sided. In both radiation chimæras and chimæras produced by injecting newborn tolerant mice with homologous lymphocytes, homologous ("runt") disease develops.[12–14] This is manifested by weight loss, diarrhœa, dermatitis, and a peculiar atrophy and granuloma formation in the spleen and lymphoid organs of the chimærical mice. Death finally results. Occasionally lymphomas also develop (see below). This reaction occurs only in those animals given homologous lymphocytes or homologous bone-marrow containing lymphocytes. Homologous liver cells, or other homologous non-lymphatic tissues, do not cause the reaction. Radiation alone or radiation together with injection of isologous lymphocytes does not lead to this reaction. Several workers have suggested that homologous disease results from sensitisation of the homologous transplanted lymphocytes by host antigens, and these lymphocytes then react immunologically against the host.[12–15] Peripheral-blood lymphocytes can cause homologous disease.[16]

An immunological theory of carcinogenesis has been proposed.[17 18]

Briefly this is that carcinogenic chemicals, viruses, or ionising-radiation agents act by combining with or altering so-called "identity" proteins or "self-markers" in cells. As a result the identity proteins become altered antigenically. This antigenically altered material acts as an autoantigen, and a locally manufactured cellular antibody develops, directed against this now "foreign" material. At the same time the agents which caused the antigenic change cause excessive stimulation and growth in the cells which have had their identity proteins immunologically altered.

Thus there exists a selective immune force which will favour the growth of those cells with the fewest identity proteins. These cells will survive and proliferate. The loss of "identity proteins" constitutes the malignant change, for it is these identity proteins which, by an interchange between adjacent cells, normally regulate the normal organised relationship between cells.[19] It is the same or closely related "self-markers" which permit the recognition of "self" and "not-self" in homografts and autografts.[20] Various degrees of tolerance can exist in the mature animal, according to the age of the fœtus at the time of arrival of the maternal lymphocytes. In the imperfect partially tolerant lymphocyte chimæra the stage is set for an immunological warfare in which a set of lymphocytes with few or no identity proteins may be selected. These lymphocytes are then malignant.

We suggest that patients with Hodgkin's disease may be maternal-to-fœtal lymphocytes chimæras of a natural variety—that is, maternal lymphocytes reached them when they were tolerant fœtuses and that the above sequence of events takes place. Murine lymphomas have developed in both radiation lymphocyte chimæras [21] and parental-to-F_1 (offspring) non-irradiated lymphocyte chimæras.[22]

Since all the transplantation antigens of the skin are also present in the lymphocytes, the chimærical patient with Hodgkin's disease should show some degree of tolerance to maternal skin.

METHOD

Five male patients with Hodgkin's disease were homografted with maternal skin. The technique was as described previously,[23] except that the split-thickness donor skin was cut

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TABLE I—DATA ON 5 CASES OF HODGKIN'S DISEASE IN WHICH HOMOGRAFTS WERE APPLIED

Case no.	Age (yr.)	Stage *	Duration of disease	Serum-γ-globulin	Recipient type	Donor type	Donor	Survival (days)	Interval between grafts (days)
1	37	III	3½ yr.	Normal	A+	A+	Unrelated	18	145
							Mother	30	
2	26	I	6 mos.	Slight decrease	B+	B+	Unrelated	14	22
						O+	Mother	30	
3	30	II	1 mo.	Normal	B+	B+	Unrelated	140	63
						O+	Mother	24	
4	29	III	1 yr.	Slight decrease	A+	O+	Mother	132‡	..
5	30	I	10 mos.	Normal	O+	..	Mother	13	..

* A. M. Jelliffe and A. D. Thomson, *Brit. J. Cancer*, 1955, **9**, 21. † From time of rejection of first graft. ‡ Patient died with graft intact.

TABLE II—TREATMENT

Case no.	Radiotherapy			Other			Graft survival	
	Site	Dose (r)	Date	Drug	Dose (mg./kg.)	Date	Unrelated	Maternal
1	Neck and mediastinum Lumbosacral area Right lumbosacral Left lumbosacral Upper abdomen Upper abdomen Lower abdomen Right jaw	3000 1650 900 1200 900 1500 1500 750	June, '54 Jan., '55 April, '56 " " " " Aug. " " " Aug. '57	Mustine Mustine Mustine	0·4 0·2 0·4	Sept., '54 June, '55 Aug., '57	Aug. 30 to Sept. 16, '57	Feb. 11 to March 10, '58
2	Right neck	3000	Jan. 3, '58 Jan. 28, "	None	..	..	Jan. 6 to Jan. 29, '58	Feb. 11 to March 10, '58
3	Anterior chest Posterior chest Left supraclavicular Left inguinal	1950 1950 3355 3000	July–Sept., '58 " " " " March, '59	..	..	..	Feb. 19 to March 15, '59	July 23 to Dec. 8, '58
4	Anterior mediastinum Superior mediastinum Retrogastric Liver Right neck Left neck	2000 1500 1300 600 1200 1200	Jan.–Feb., '58 Nov.–Dec., '58 Jan., '59 Feb.–March, '59 " " " "	Prednisone 'Cytoxan'* "	.. 8×6 i.v. 8×5 i.v.	Feb.–March, '59 March, '59 " "	..	Dec. 11, '58, to April 22, '59
5	Anterior chest Right upper chest and neck Left supraclavicular and neck Left posterior neck	1800 1800 1800 1800	Dec., '58–Jan., '59 " " " "	..	..	..	..	March 18 to April 1, '59

* Cyclophosphamide.

free-hand from the upper lateral thigh of the maternal donor. The grafts that showed prolonged gross survival were serially biopsied and stained by the Feulgen technique and hæmatoxylin and eosin. The biopsy specimens in case 3 were fixed in 10% formalin and those in case 4 in alcohol formol acetic acid (Davidson's solution).

RESULTS

The gross survival-times of the maternal skin, and the survival-times of unrelated skin grafts previously applied, are shown in table I. The treatment received by these patients is shown in table II, and the proportion of female chromatin marker in biopsy specimens in table III.

Two of the five patients showed prolonged survival of the maternal homografts. In case 3 the Feulgen preparations were of poor quality and the female marker material was present in only 1–3% of cells; but serial biopsies in case 3, stained with hæmatoxylin and eosin, showed decline of the initial inflammatory reaction followed by intense lymphocytic infiltration at the time of gross rejection (140 days), indicating that the original graft was being rejected at this time. In case 4 a high proportion of female chromatin-positive cells in all the biopsy specimens, indicated survival of the maternal graft.

DISCUSSION

Homologous disease and Hodgkin's disease have the following characteristics in common: weight loss, skin manifestations, hæmolytic anæmia, and in certain cases unexplained death. Kaplan and Smithers have also noted these similarities.[24]

24. Kaplan, H. S., Smithers, D. W. *Lancet*, 1959, ii, 1.

TABLE III—DURATION OF MATERNAL-SKIN HOMOGRAFTS AND PROPORTION OF FEMALE CHROMATIN MARKER IN BIOPSY SPECIMENS

Case no.	Date	Duration of graft (days)	% chromatin-positive
3	July 21, '58	0*	20
	Sept. 8, "	49	1
	Oct. 9, "	80	Not done
	Dec. 8, "	140	3
4	Dec. 11, '58	0*	22
	Dec. 31, "	20	20
	Jan. 23, '59	43	Technically imperfect
	Feb. 27, "	78	28
	April 13, "	123	38
	April 22, "	132	43

* Maternal skin obtained at time of homografting the patient.

Unfortunately, the temperature of animals with homologous disease has not been reported. The lymphoid atrophy in homologous disease is often preceded by hyperplasia and granuloma formation with increase in weight of the liver and spleen.[25 26] The absence of frank homologous disease in the "potential" patient with Hodgkin's disease can be explained by the very large "antigen" excess in relationship to the small amount of postulated homologous lymphoid tissue which is initially present.

The apparently long survival of lymphocytes judged by isotopic marker techniques has been given two interpretations. One is that the lymphocyte itself survives intact for long periods. The other interpretation is that it is not the entire lymphocyte, but only "chunks" of desoxyribonucleic acid (D.N.A.) that survive for a long time, and that these "chunks" of D.N.A. are reutilised to form new lymphocytes. Morphological [27] and theoretical [28] evidence for this last hypothesis has been advanced. If this second interpretation is correct, and if maternal lymphocytes do gain entrance into the fœtus, then the lymphocyte D.N.A. of the fœtus can itself become chimærical, being composed of the D.N.A. of the mother and also of the fœtus.

Some of the murine radiation chimæras developed lymphomas which were composed of the donor-strain lymphocytes.[21] If donor (maternal) lymphocytes could become malignant in patients with Hodgkin's disease, this disease could be treated with polycylic tumour-inhibiting (T.I.) hydrocarbons.[17 18] These are effective against tumours only where some histocompatibility difference exists between host and tumour. Green has reported preliminary favourable results with T.I. compounds in patients with Hodgkin's disease.[29]

We are well aware of the several possible explanations, besides acquired tolerance, of long-continued survival of maternal skin in patients with Hodgkin's disease. In a previous study, however, in no case of Hodgkin's disease did unrelated skin survive for more than 34 days [23];

25. Simonsen, M., Engelbreth-Holm, J., Jensen, E., Poulsen, H. *Ann. N.Y. Acad. Sci.* 1958, **73**, 834.
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many of these patients were critically ill and had received extensive treatment. Many more patients with Hodgkin's disease will have to be grafted, some with maternal skin and some with paternal skin. Also, data concerning the survival of maternal-skin homografts in healthy people as well as patients with other chronic illnesses will have to be obtained. The validity of the present hypothesis can be investigated in other ways as well. We hope that this report will act as a stimulus for further studies.

We acknowledge the technical assistance of Miss Nancy Whitehead. We wish to thank Dr. H. Stambaugh, Dr. M. Lewin, and Dr. M. Flynn for performing the skin grafts on these patients, and Dr. J. Wolf, Dr. P. Cooper, and Dr. T. Spaet for their cooperation and support.

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SERUM FATTY ACIDS AFTER FATAL HEART-ATTACKS

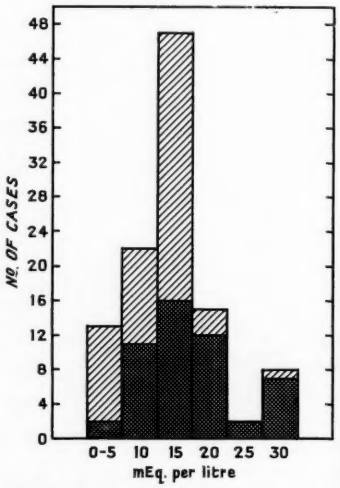
MANY fatal heart-attacks, while demonstrably due to ischæmic heart-disease, present no recent morbid-anatomical changes in myocardium or arteries to account for the sudden stoppage of the heart's action. In a survey in which clinicopathological enzyme tests were used to elucidate the nature of these attacks, blood-lipids were examined also. In 50 fatal cases of ischæmic heart-disease and 57 control subjects the simple colorimetric method of Stern and Shapiro [1] has shown serum-fatty-acid levels which may have a bearing on the mechanism of these heart-attacks.

In this series four pathological groups were separated without prejudice to possible interrelationships. They are (*a*) simple coronary atherosclerotic narrowing or occlusion, (*b*) fibrosis of the myocardium without recent change or thrombosis of the arteries, (*c*) myocardial necrosis whether or not accompanied by coronary thrombosis, and (*d*) cases in which an arterial thrombus was demonstrated without naked-eye evidence of recent myocardial changes.

The mean normal value for serum fatty acids by Stern and Shapiro's method in young healthy adults is about 10 mEq. per litre. In the four groups described above the mean values were (*a*) 14·2 mEq. per litre (27 cases), (*b*) 12·6 mEq. (6 cases), (*c*) 15·5 mEq. (11 cases), and (*d*) 16·1 mEq. (6 cases). The mean value in these 50 cases was 14·7 mEq. per litre, whereas the mean for the 57 controls was 9·9 mEq. The difference between these means is highly significant ($t = 6{\cdot}1$; $p < 0{\cdot}001$). The controls were further divided into nine disease groups of which only two were suggestively abnormal, both yielding low values. These were the cancer group (10 cases), with a mean of 7·5 mEq. per litre, and the group of cardiac deaths not due to coronary-artery disease (12 cases), with a mean of 8·4 mEq.

When the distribution of the results is examined (see figure), it is seen that 10 out of 11 values higher than 17 mEq. per litre are from cases of cardiac ischæmia. The 1 control with a high value was a patient with a pelvic abscess who had died from carbon-monoxide poisoning. Furthermore, the values in the cardiac-ischæmia cases show a diphasic distribution whereas the controls are approximately normal in distribution. 5 of these 10 high values belonged to the group dying from simple coronary occlusion.

The level of serum fatty acids in cadavers is only slightly affected by decay.



Distribution of serum-fatty-acid values from 107 cadavers.

The solid columns represent values from 50 cases of ischæmic heart-disease, and the shaded columns the values from 57 controls.

The mean values in successive 12-hour periods after death were 9·7 mEq. per litre (17 samples), 12·2 mEq. (35 samples), 12·7 mEq. (20 samples), and 15·0 mEq. (18 samples). The mean value during the period 4–6 hours after death (5 samples) was 8·8 mEq. per litre. Thus there was a slow rise starting soon after death. These figures exaggerate the rise, since the cancer cases, which had low values, were mostly examined in a hospital mortuary soon after death, while cases of sudden death were examined in the public mortuaries rather later. Even so, because the difference in the mean values attributable to differences in the mean time of examination between the deaths from cardiac ischæmia (43·5 hours) and the remainder (37 hours) is only about 0·6 mEq. per litre, this cannot account for the significant differences recorded above. After 48 hours the mean serum-fatty-acid level fell slightly (10·9 mEq. per litre; 13 samples) and after 60 hours it rose again (14·0 mEq.; 4 samples). This dip at the end of the accumulation curve is characteristic of several organic substances in cadaver blood, having been seen with hæmoglobin, phenolic substances, and the changes in opacity of deproteinised serum to ultraviolet light.[2] In a large series, this reduces further the mean change due to time after death, and therefore undue regard need not be paid to this change.

There was no significant difference between the mean ages of the cardiac-ischæmia group (65 years) and the control group (63 years).

The condition commonly recorded on death certificates as " coronary occlusion " is probably a syndrome in which several different factors may be the cause of the fatal insufficiency. The high serum-fatty-acid values encountered in this series of cases of ischæmic heart-disease, their similarity to those from cases with recognisable recent organic changes, their dissimilarity from most of the control values, and, particularly, their diphasic distribution suggest that high levels of serum fatty acids may be one of these factors. A larger series will enable the effects of selection to be excluded with greater certainty, and it remains to be seen whether any particular fatty acid is regularly responsible for the high values shown by the non-specific colour reaction of Stern and Shapiro's method.

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Medical Societies

AMERICAN SOCIETY OF HÆMATOLOGY

THE second annual meeting of this society was held in St. Louis, Missouri, on Nov. 22–24.

Antibody Synthesis

Dr. HERMAN EISEN (Pennsylvania), who also presented the views of his colleague, Dr. FRED KARUSH, said that the two possible modes of antibody formation were the " instructive ", requiring the presence of the specific antigen for the formation of specific antibody, and the " selective ", which implied the prior existence of specific antibody-forming cells, the " clone " of Macfarlane Burnet. The qualities of a protein molecule, in one or more of which specificity must reside, were aminoacid sequence, helicity, the folding of the helix, and degree of polymerisation. There was at present insufficient evidence to indicate which theory was correct and which qualities of a protein antibody conferred specificity.

Dr. D. W. TALMAGE (Colorado) inclined to the selection theory, which implied that specific antibody formation was determined spontaneously and that corresponding antigen stimulated synthesis by, and probably reduplication of, the cell carrying this " natural template ". Studies of tolerance and immunity suggested, on this theory, that any antigen must have opposite effects on its corresponding clone at different stages of the latter's development.

Dr. E. S. LENNOX (University of Illinois) had developed a technique for the determination of antibody production by single cells, using lymph-node cells immunised to various bacteriophages, suspended in droplets, and assaying the power of these cells to inhibit phage activity. About 20% of single cells could make two antibodies contemporaneously. What appeared morphologically to be lymphocytes were only about half as active in antibody production as what seemed to be plasma cells, but such characterisation was not conclusive, for the cell types might not be stable and in these experiments were not quite " caught in the act ". From these findings Dr. Lennox argued against the selection theory, though the possibility that a single clone might be capable of producing more than one specific antibody could not be ruled out.

Dr. A. COONS (Harvard) discussed rate of antibody production in primary and secondary response. Burnet and Fenner had shown that rise in antibody titre in the secondary response was almost logarithmic, and Dr. Coons and his colleagues therefore examined lymph-nodes during both types of response, using a fluorescein label to demonstrate the presence of antibody in cells. There was scarcely any labelling after primary antigen injection; after a second injection many more cells stained up, though none contained much antibody. The positive cells in the node were not clumped in a clone. Further experiments were then done to determine whether, in mice, the time between primary and secondary antigen inoculation was directly proportional to the size of the secondary response. The secondary response levels off, however, after about 20 days, and Dr. Coons speculated that the continuing presence of antigen was required for the clone to continue to multiply. At this point discussion arose as to why animals could not be converted almost exclusively into antibody. It was assumed that at a critical level further antigen was prevented by antibody already present from exerting a stimulus to further antibody formation.

In a comprehensive review of immune tolerance and autoimmune disease Dr. R. E. BILLINGHAM (Pennsylvania) speculated on the late breakdown of immune " tolerance " as a is for autoimmune disease. Normally maintained " physiological quarantine ", as in the thyroid, might break down, or late maturation, as in the breast or testis, might occur, so that tolerance might not have been acquired; or perhaps some lymph tissue might exist in a state of " quarantine ", possibly in the thymus, and constitute a threat to earlier acquired tolerance. In comparing the ability of cells of various origins to produce " tolerance " on the one hand, and " runt disease " on the other, Dr. Billingham stressed that both the type of cell and the numbers in the inoculum were important. Lymphocytes seemed to be effective in producing both phenomena, but thymus cells might produce " runt disease" but not " tolerance ".

Ætiology of Leukæmia

Dr. JOSEPH BEARD (Duke) followed his own aphorism that " people get up to talk about human leukæmia and the first thing you know they're talking about mouse or chicken leukæmia ". He had found what he felt must be virus particles in thin sections of blast cells in acute human leukæmia observed with the electron microscope in only 1 case in 12, whereas Dmochowski in Houston had 50% positives. In fowl leukæmia, however, no virus particles were seen either, unless the blast cells were grown in culture, when they became loaded. Dr. LUDWIG GROSS (New York) pointed out that virus might not always show up under the electron microscope and what did show up might not be virus. Dr. S. SCHWARTZ (Chicago) developed his theme that variations in incidence of induction of leukæmia, using material from patients with leukæmia, might be due to different balance between virus and inactivating factors.

Radiation as a factor was discussed by Dr. EUGENE CRONKITE (Brookhaven). He presented arguments against interpreting any data at present available as showing that irradiation was leukæmogenic. He seemed not to be wholly convinced by his arguments himself, and finally agreed that at present a policy of playing safe was probably the best working basis.

Dr. ROBERT HEYSSEL (U.S. Public Health) presented the most recent figures for the incidence of leukæmia in the Japanese atom-bomb areas. The errors in assessing dosage of radiation were recognised as being very great, and there was clearly much divergence of opinion about the significance of conclusions which have been drawn from earlier figures.

Dr. GEORGE WOOLEY (Sloan-Kettering Institute) summarised what is known about chemical and hormonal factors in leukæmogenesis in animals, emphasising the importance of the thymus for induction of leukæmias and tumours, and mentioning Metcalf's claim that a lymphocyte-stimulating factor (L.S.F.) was found in plasma of mice which later developed lymphoma. Dr. J. TRENTIN (Houston) mentioned that rises in L.S.F. had been observed after irradiation and he postulated that L.S.F. could be the mediating agent for leukæmia.

The epidemiology of human leukæmia was then briefly discussed, and the point was the need for good studies in this field. At this stage the chairman, Dr. JACOB FURTH (Roswell Park), took a show of hands of those who believed that a virus, radiation, hormonal and chemical factors, or genetic factors had been a causative factor in any one of their cases of leukæmia. Of a total of about 600, 26 raised their hands for radiation, 15 each for chemical and genetic causation, and viruses came a poor fourth.

Notable among other contributions was a group of observations on transformation of human leucocytes into histiocytes, fibroblasts, and fat cells in subcutaneous diffusion chambers made of ' Micropore '. Dr. N. L. PETRAKIS (San Francisco) showed pictures of his preparations, with collagen fibres forming in chambers in which only cells from the buffy coat had been placed.

Dr. E. DONNALL THOMAS' group (Cooperstown) had been studying hæmoglobin synthesis in fœtal tissues. It seems that adult hæmoglobin is formed from the earliest period (about 9 weeks) onwards and that all organs producing hæmoglobin produce both the adult and fœtal type in proportions constant for the particular tissue.

Dr. S. PIOMELLI (Boston), in studying " secondary disease " in X-irradiated rabbits, transfused with homologous bone-marrow, found that transfusion immediately after irradiation was life-preserving; 12 hours later it was ineffective. Incomplete red-cell antibodies were found in the serum of the runts so produced, with a positive Coombs test 3–7 weeks

later. Red-cell survival in these animals was always reduced but full-blown secondary disease was rare and less severe than in rodents. Since rabbits are not pure-bred these results were considered encouraging. Dr. W. HOLLANDER (Oak Ridge) pointed out that mice with spleen-induced "runt disease" have a leucopenia but not a positive Coombs test.

Dr. W. DAMESHEK (Boston) and his colleagues presented data showing that so far no success has been obtained in the treatment of aplastic anæmia with bone-marrow transfusions.

Reviews of Books

Medical Surveys and Clinical Trials

Editor: L. J. WITTS, C.B.E., M.A., M.D., SC.D., F.R.C.P., Nuffield professor of clinical medicine, University of Oxford. London: Oxford University Press. 1959. Pp. 328. 35*s*.

Professor Witts has collected the experience and outlook of many experts on population surveys, follow-up studies, and therapeutic trials. His co-authors are all well known and their contributions are of great interest. All who wish to undertake such large investigations should consult this book, which indicates both the value and the difficulties of population surveys. The widespread and proper use of statistical method, so desirable, is not always easy to achieve, and often enormous numbers of subjects have to be studied before an answer becomes clear. Almost everyone has been impressed by the statistical evidence which proved the value of streptomycin in pulmonary tuberculosis, which linked cancer of the lung with cigarettes, and maternal rubella with fœtal abnormalities: but these were all elaborations following strong clues from previous clinical observation and experience. A well-known survey of blood-pressure in a population led to much controversy and revealed the difficulties of tackling a problem by survey methods alone. The question seems to have been clarified by the application of knowledge based on extensive clinical and pathological experience, and once again the professional habit of dividing normal from abnormal systolic blood-pressure at about 160 mm. Hg appears to be reasonable. In short, the statistical approach may be quite unintentionally confounding unless regulated by strict attention to the existing body of knowledge. Even "high statistical significance" is not proof, unless the idea finds other scientific support.

The survey method is often extremely costly from its very magnitude, and sometimes the problems posed are capable of solution by precise laboratory methods on much smaller numbers. The open mind free from bias, beloved of the statistician, can conceal medical amateurishness or even ignorance, while the good clinician is discouraged from detailed observation and questioning by the requirements of "double-blind" trials. Subjective judgments inevitably come in, and in one blood-pressure survey in Bergen there was an obvious inclination to record the pressures in the nearest round figure. Observer error in all clinical matters is a well-recognised phenomenon, and if we could believe all that has been written about it, it is amazing that diagnosis is as satisfactory as it seems to be in practice. In large population surveys complete individual case analysis is impossible and records are often made of some single measurement or parameter. If our predecessors of the year 1800 had surveyed "anæmia" based on hæmoglobin only, what light would have been cast on blood disorders? More recent attempts to define a mutation-rate in hæmophilia become of little value as we realise the number of concealed cases with only slight reduction of antihæmophilic globulin. Thus the modern view drives us back to the laboratory work of the scientists for inspiration and guidance. Without the backing of a well-founded idea, surveys are apt to be sterile, and the best statisticians cannot extract the answers.

One or two of the contributors to this monograph pay little attention to the laboratory approach: the editor himself says "the location of clinical scientists in hospitals . . . invites the danger of an increasing impoverishment of ideas . . . much current research is trivial in conception". This is a challenge which many will find provocative. All who are interested in surveys and particularly those who imagine they are easy ways to dramatic conclusions should read this book and take warning.

Aldosterone in Clinical and Experimental Medicine

E. J. ROSS, M.D., PH.D., M.R.C.P., senior lecturer in medicine, University College Hospital Medical School, London. Oxford: Blackwell Scientific Publications. 1959. Pp. 144. 22*s*. 6*d*.

ALDOSTERONE was discovered only five years ago and is still, and likely to remain for some time, the focus of much research. It has attracted interest in many countries because its role in controlling electrolyte metabolism is of concern to biochemists, physiologists, and clinicians. Dr. Ross, who has worked in Dr. George Thorn's laboratories at the Peter Bent Brigham Hospital in Boston, is in a strong position to discuss aldosterone from every possible aspect, and he does so very ably in this concise monograph.

From a basis of 539 references he discusses all that is known about the hormone, and he has done a great service to all kinds of workers in this field by his review of the extensive literature. He writes clearly and factually, and it is not until the last chapter, on the role of aldosterone in human homœostasis, that he allows any speculation. Dr. Ross is not afraid to say what is not known and to point the way for future research.

This book is an excellent summary of the position at half-time. We hope Dr. Ross will be able to report the outcome of the game when the final whistle is blown.

The Principles of Humane Experimental Technique

W. M. S. RUSSELL, M.A., D.PHIL., UFAW research fellow, department of zoology and comparative anatomy, University College London; R. L. BURCH, hon. UFAW research assistant. London: Methuen. 1959. Pp. 253. 30*s*.

THE object of this book, sponsored by the Universities Federation for Animal Welfare, is to ensure that experiments on animals involve the least possible inconvenience to them, while increasing the scientific value and reliability of those experiments which are performed.

The authors summarise the matters to which they draw attention as follows: (1) belated knowledge of the relative numbers of species used; (2) persistent use of the Friedman test; (3) delay in the initiation of microbioassay; (4) delay in the exploitation of statistical methods; (5) delay in the rationalisation of breeding methods for uniformity; (6) delay in noticing published effects of environmental factors; (7) delay in the application of psychosomatic principles; (8) conservatism in the choice of laboratory species; and (9) the guarded approach to several aspects of toxicity testing. These are all questions of moment to the research-worker, who, however, it should be said in justice to him, recognises them all.

The authors have presented their work as if it were a review article, and have copiously burdened the text with references, most of which are not likely to be challenged by the reader of a book of this type. For this reason it may fail to reach the audience to which it is directed. Its purpose is admirable, and its matter unexceptionable. But it is not easy reading: a shorter and more dogmatic paper would have made a stronger impact, and lost none of its authority.

Pharmacopœa Internationalis (*Supplement*. Geneva: World Health Organisation. 1959. Pp. 224. 25*s*. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1).—The first edition of the *International Pharmacopœa*, volumes I and II of which appeared in 1951 and 1955, is completed by this supplement containing a further 94 monographs and 17 appendices.

THE LANCET

LONDON 2 JANUARY 1960

Into the '60s

" He who plays a part in events is the last to know their real importance; and the moment he tries to seize their purport, and to take a conscious part in them, his actions are barren of result."

Describing the situation after the fall of Moscow in 1812, TOLSTOI wrote of the uselessness of people who tried to understand what was going on, compared to the usefulness of the army, which did not trouble its head with large affairs but continued to think about " the next quarter's pay, the next halting-stage, of Matrechka, the vivandière, and so forth ".[1] Similarly in Medicine one may argue that the only useful thing is to get on with the job—with the good work that will make all the difference to some individual patient or (if an investigator has luck or genius) may transform the outlook for thousands or millions, as happened through the discovery of penicillin and streptomycin.

But TOLSTOI overstated his case. Few armies remain long in the field unless there is at least enough intelligent planning to ensure that they receive their pay, their food, and their ammunition; and few armies win battles unless arrangements are made for them to be in the same tract of country as the enemy. In the war on disease the same is broadly true; and, because this war becomes steadily more elaborate, we cannot avoid more organisation of one sort or another. We all know, of course, that what ultimately matters in Medicine is the care of the patient and the prevention of disease; but the kind of organisation matters greatly, too, because a defective one will not supply the medical troops with what they need and will not deploy them where they are wanted most. In this country our biggest attempt at medical organisation—the National Health Service—has not proved nearly so restrictive as many of us feared, but it is not yet as constructive as some of us hoped: it has preserved most of what we valued but it has failed to add what we might value more. On the performance of its difficult first decade, the mark it deserves is perhaps an Oxford β (opinion will differ on whether a $\beta-$ or a $\beta+$); and the question to be decided in the '60s is whether the burden of routine will keep it at this merely respectable standard or whether it will achieve the α of which it is capable. To do so it needs, of course, more money; but it also needs more of the rare kind of discontent that gets things done. In the '60s scientific Medicine is likely to accelerate its startling progress, and at all levels we shall need corresponding flexibility and enterprise. Considering the difficulties, our service is good and economical; but the public will still have bought it too dear if, under Government auspices, it loses the adaptability which is a sine-qua-non for biological success in a changing environment.

Some of our present problems are those of the particular kind of organisation we have created. For example, something will sooner or later have to be done to make the Ministry of Health less like an ordinary Government department and more like the nerve-centre of a complex public and professional service. (The Government so far show no sign of having read the Acton Society and Sir GEORGE SCHUSTER [2] on this far from negligible subject.) Something will have to be done, too, to bring the English regional hospitals and the teaching hospitals more closely together, in the interest of both. (Probably the time has come to begin an inquiry into the size of the regions, the function of regional boards and hospital management committees, and the simplification of their administrative machinery.[3]) Again, something will have to be done about remuneration in the health service—" the next quarter's pay "—on which the Royal Commission should be reporting at the end of February. But beyond such local and relatively soluble problems are more universal and intractable ones arising mainly from the rapid industrialisation of medical work. For instance, even in the prosperous United States, a great many hospitals find it as hard as many of ours to maintain a proper junior staff. Far more important, the future of personal medical care remains uncertain everywhere except in those Communist countries where the general practitioner has been frankly abolished in favour of the small specialist team. Scarcely anywhere, as yet, does the prevention of disease get as much attention as its treatment. And in Medicine, as in international relations, there is an ever-increasing risk that uncontrolled science will neutralise humanity.

In the past decade we in this country have been making the overdue transition from a commercial type of medical practice to one in which the patient's needs can be considered first, last, and all the time. That in itself is an achievement; and one in line with professional tradition. Furthermore, whatever we may feel about our national deficiencies, monetary or mental, we still have in Britain an exceptionally favourable environment for practising and improving and enriching medicine. Our country is geographically small but intellectually extensive, and its political stability is such that it can accept considerable changes without disruption. Unhappily, with that innate respect for the past which the past, as a whole, so seldom deserves, many members of our profession, both old and young, are inclined to underestimate the current British contribution to Medicine. The truth, however, is that though there are some things we cannot do, there are many—both scientific and social—which we do better than anybody else. From those individual pursuits and personal preoccupations which TOLSTOI commended we can still confidently count on our quota of discoveries—usually no more than tiny points of light, but just occasionally some great

1. War and Peace. Everyman's Library edition; vol. iii, p. 176. London, 1917.

2. See *Lancet*, 1959, i, 349.
3. *ibid.* 1958, ii, 27.

flash. And likewise from a certain national ingenuity in that art of organisation which TOLSTOI was inclined to underrate, the public can expect further benefit because good organisation promotes good use of new knowledge.

If one may judge by what happened in the first six decades of this century, nobody need fear lack of incident or interest in the seventh. Least of all, perhaps, anybody with insight into diseases and health, and a liking for the people who have them.

Genesis of Cardiovascular Murmurs

THE presence of a murmur does not depend on any vital property of the heart or blood-vessels. Its primary cause is an alteration in the nature of flow of the blood itself; the solid structures forming the boundaries of the fluid are thrown secondarily into a state of greater or lesser vibration. These conclusions, set out by CORRIGAN [1] for these columns some years ago, have not been seriously challenged.

CORRIGAN pointed out three anatomical conditions which tend to give rise to murmurs: constriction of the lumen of a vessel, a constricted orifice leading to a normal cardiac chamber or vessel, and a normal orifice opening into a dilated chamber or vessel. For such murmurs, and for the murmurs of high-output states and those accompanying abnormal anatomical communications, the altered character of flow may be turbulent [2] (fluid particles moving at random), more or less orderly with the production of eddies (vortices),[3] or associated with a periodic vortex-ring pattern [4] (musical jet) or with the formation and collapse of bubbles of dissolved gas or of water vapour (cavitation).[2]

In a long uniform cylindrical tube, turbulence develops in a homogeneous fluid flowing at a constant rate when the Reynolds number VD/ν (velocity $\times$ diameter/kinematic viscosity) exceeds 1900.[2] The corresponding critical Reynolds number for blood is 1940$\pm$ 160.[5] REYNOLDS [6] noted that with varying flow, and with steady flow in a channel which converges or diverges or which has a rough wall or non-circular section, the critical velocity associated with the onset of turbulence is not necessarily determined by this function VD/ν. MCDONALD [7] doubts whether turbulence is as important a source of murmurs in the cardiovascular system as was once held; and now BRUNS [8] has expressed the view that the acoustic energy generated by turbulence is inadequate to account for audible murmurs. Although he describes various ideas in support of this view, the evidence—particularly on the interaction between a turbulent fluid boundary layer and a vessel or cardiac wall—must be regarded as incomplete.

The existence of eddies or vortices (generated, for example, by an obstruction in the path of flow) may be causally related to murmurs [7] since a considerable pressure drop may exist in their centres. BRUNS [8] discusses the analogous phenomenon of Æolian tones [9 10] (a familiar example of which is the singing of wires in a wind), and the associated rhythmic shedding of eddies [11] which stem from a cylindrical wire placed in the path of a constant flow of air. These have been studied extensively.[12–15] Such eddies in a fluid medium consist of localised spinning masses of fluid; these pass downstream for some distance before dispersing. The rate of development of eddies is more or less regular, and since this generation occurs alternately from each side of the obstacle, two rows of vortices are formed downstream. Sound is emitted from such a wake, and the frequency or pitch of the tone corresponds to the rate of shedding of vortices.[3] This frequency is proportional to the ratio of the fluid velocity to the diameter of the cylindrical wire.[10] Slight irregularities of form of the cylindrical wire give rise to a frequency spectrum of sound—i.e., noise.[8] BRUNS draws attention to the movement of the bulk of fluid comprising the wake, rather than the vortices themselves, as the source of acoustic power. Similar sounds have been noted from the wakes generated by vanes in flowing water.[16]

The rhythmic disturbance of an axially symmetrical jet, associated with the formation of ring-vortices,[17] is a related phenomenon.[18–20] SAVART [20] in 1854 described a loud tone heard when a jet of water issues from a small orifice into air or water. The frequency of generation of ring-vortices from such an orifice is related to the velocity in a somewhat stepwise fashion,[20] or, more generally, to the Reynolds number,[21] and tends to increase with increasing velocity or diminishing jet diameter. The same vortex pattern develops for larger orifices, even those almost filling the lumen of a vessel.[8]

Considerations of acoustic energy,[7 8] of the frequency, intensity, and transmission of particular cardiovascular murmurs,[8] and of KÁRMÁN's classical theory [13 22] of "vortex streets" point to the importance of such eddies in the production of murmurs. The low pitch of downstream-propagated murmurs (of mitral stenosis and aortic stenosis, for example) and the higher pitch of upstream-propagated murmurs (of mitral insufficiency) are compatible with this concept.[8] The model experiments of BRUNS are in some respects confirmatory; for example, the intensity of low-frequency components of the murmur generated by a constriction in a vessel increases at first as the stenosis is made smaller; but for very small orifices the intensity falls off again, as predicted by BRUNS on the basis of vortex theory.

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21. Anderson, A. B. C. *J. acoust. Soc. Amer.* 1955, **27**, 1048.
22. Spitzbarth, von H., Weyland, H., Gersmeyer, E. F. *Z. Kreisl. Forsch.* 1958, **47**, 965.

EULER [23] foreshadowed the importance of cavitation in hydraulics in 1754. Reynolds cavitation [6 24 25] associated with fluid flow through a constriction is unlikely to be a common source of significant cardiovascular sound since the pressure differential required across the stenosis (about 350 mm. Hg) is rarely achieved).[8] Gas-entrained bubbles would emit frequencies above the important components of most murmurs.[26] Nevertheless, the possible existence of a different form of cavitation [7] associated with the low pressures at the centres of vortices cannot be disregarded.

The clinical importance of understanding the mechanism of genesis of murmurs was recognised by CORRIGAN. Clearly the story is not yet complete. Meanwhile we should recognise the fallacy of simply equating turbulence with murmur production, the need for considering further the consequences of the pulsatile character of flow, and the interplay between the primary disturbance in the blood and the secondary disturbance of the boundaries.

A New Familial Abnormality of Red Blood-cells

IN the past few years information has been accumulating about an entirely new type of intrinsic abnormality of red blood-cells—an enzyme deficiency which is usually harmless unless the cells are exposed to one of several drugs or ingested substances.[27] The existence of this defect was discovered during an investigation of the acute hæmolytic anæmia caused by primaquine—an 8-aminoquinoline drug, chemically similar to pamaquin, used for the treatment of malaria. Cases of this anæmia caused by pamaquin had been described by MANSON-BAHR [28] in 1927, by CORDES [29] in 1928, and by many others later. The patients were extensively investigated by current techniques, but the results were negative: no constant immunological abnormalities were detected; there was no abnormality of red-cell fragility and no sickling; and there was no correlation between the plasma level of pamaquin or primaquine and the degree of hæmolysis. But there were some positive observations. In a sensitive patient primaquine always induced hæmolysis except for a time after a dose, during which further doses did not cause hæmolysis. Primaquine sensitivity is not common; but it is relatively more frequent among Negroes, and British troops have been observed to be less susceptible than Indians or Burmese. The clinical course of the hæmolytic reaction is very characteristic. In a susceptible person no evidence of hæmolysis appears for the first two to three days, and this latent period occurs whether primaquine is being given for the first or a subsequent time. The signs include hæmoglobinuria, icterus, and a rapid decrease in red cells and hæmoglobin; reticulocytosis develops and BEUTLER et al.[30] pointed out that Heinz bodies appear in many of the red cells. The Coombs reaction for adsorbed antibodies remains negative. The acute phase lasts about a week, and recovery ensues, even if the administration of primaquine is continued. This apparent tolerance lasts for a few weeks after withdrawal of the drug, and another dose then produces exactly the same sequence of symptoms and signs. BEUTLER [27] notes that some other drugs such as acetanilide, sulphanilamide, and nitrofurantoin cause a similar clinical picture of hæmolytic anæmia in susceptible patients.

Such a drug-induced hæmolytic anæmia could be due either to the production in the blood of abnormal factors that affected red cells, or to some abnormality of the red cell itself. In 1954 DERN et al.[31] showed that sensitivity to primaquine was due to an intrinsic abnormality of the red blood-cells. Red cells from a sensitive person were labelled with radio-chromium and infused into a non-sensitive person; primaquine (30 mg. daily) was given to this non-sensitive recipient, and the labelled red cells were rapidly and selectively destroyed. Conversely labelled red cells from a non-sensitive person transferred into a sensitive patient were unaffected by administration of primaquine. The primaquine-sensitive cells were fully investigated by BEUTLER, DERN, and their co-workers. None of the previously known red-cell abnormalities were present, and eventually investigation of the Heinz bodies provided the clue. When sensitive red cells were incubated in the presence of oxygen with certain reducing substances, such as acetylphenylhydrazine and ascorbic acid, they developed a pattern of Heinz bodies—denatured protein particles—which was consistently different from that appearing in non-sensitive cells.[32] BEUTLER et al. described a test for detecting sensitive cells: heparinised blood is incubated for four hours with a pH 7·6 phosphate buffer, containing 200 mg. glucose per 100 ml. and 100 mg. acetylphenylhydrazine per 100 ml.; wet preparations are stained with crystal-violet and observed under the microscope. In a sensitive person more than 40% of the cells contain 5 or more Heinz bodies, whereas in almost all non-sensitive persons less than 30% of the red cells contain this number. These findings have been confirmed by others and noted in some other drug sensitivities; and LARIZZA et al.[33] found the same sensitivity in the red cells of patients with favism—the curious hæmolytic anæmia, well known in Sardinia and southern Italy, that develops in some who eat broad beans (*Vicia fava*) or are exposed to the pollen of the broad-bean flowers.

The next step was the demonstration by BEUTLER et al.[34] that the glutathione content of sensitive red cells tended to be below normal and that poisoning of non-sensitive cells with iodoacetate, which binds sulphydryl groups, caused them to react like sensitive cells in the Heinz-body test. Later these workers found that when red cells from primaquine-sensitive patients were incubated for two hours with acetylphenylhydrazine the

23. Euler, L. Cited by V. A. McKusick and H. K. Wiskind (footnote 24).
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34. Beutler, E., Dern, R. J., Flanagan, C. L., Alving, A. S. *J. Lab. clin. Med.* 1955, **45**, 286.

glutathione content fell sharply from a starting level of about 50–70 mg. per 100 ml. of red cells to less than 12 mg. per 100 ml.; whereas with cells from non-sensitive persons with a normal starting level of 50–80 mg. per 100 ml. the figure remained above 44 mg. per 100 ml. This observation has been developed into a "glutathione-stability test" by means of which red blood-cells affected by this abnormality can be readily detected.[35] The glutathione content of red cells was determined by a modification of the colorimetric technique of GRUNERT and PHILLIPS [36] based on the development of a rose-coloured complex with sodium nitroprusside and its stabilisation with cyanide. The reason for this instability of glutathione is thought to be an enzyme deficiency; BEUTLER et al.[37] have carried out experiments that suggest that there is a deficiency of glucose-6-phosphate dehydrogenase, but other enzymes concerned with carbohydrate metabolism in the red cells may also be involved.

The glutathione-stability test has been tried in many blood diseases, and in most the results are negative. Positive results are, so far, limited to the hæmolytic anæmia induced by certain drugs in sensitive individuals and in favism. The results with favism are of much interest, since it is known to be an inherited disease. SANSONE and SEGNI [38] and LARIZZA et al.[33] in Italy and SZEINBERG et al.[39] in Israel found that the cells in patients with favism showed glutathione abnormalities like those in primaquine-sensitive patients. SANSONE and SEGNI eventually found that in patients with favism the red cells gave positive results with the Heinz-body test and the glutathione-instability test of BEUTLER, and they showed a deficiency (often complete) of glucose-6-phosphate dehydrogenase. These workers and others since have detected this enzyme abnormality of the red cells in apparently unaffected relatives of patients with favism, and the defect was shown to be less complete in females than males. SANSONE concluded that the defect was inherited as a dominant partially sex-linked character. CHILDS et al,[40] in Baltimore, have carried out an extensive genetic study of the probably identical primaquine-sensitivity of red cells.

They selected Negroes for this study since the defect is known to be commoner among them than among the white population, and they used the glutathione-stability test for sorting. In a group of 144 Negro males and 184 Negro females, the prevalence of sensitive individuals, or "reactors", was found to be about 14% in males and 2% in females; but in addition 5% of females showed partial or "intermediate" sensitivity. Reactors were found in 16 families, and all cooperative members of these families were tested—90 females and 73 males. The results showed again a preponderance of reactor males, but female reactors and intermediates together almost equalled the males. Affected members were found in an many as three generations. In family 1, for example, a female reactor was found in generation 1, but her husband was not tested; of her 5 children, 1 male and 1 female were reactors; the male married a normal female and had a normal son and a reactor daughter; this daughter married a normal male and had 4 daughters of whom 3 were intermediate reactors; 1 of these has married a normal male and had 6 children, all normal; in addition 1 of the apparently unaffected females of the second generation married a normal male and had an intermediate reactor daughter. CHILDS et al. suggest that the most likely mode of inheritance is "sex-linkage with incomplete dominance", thus agreeing with the results from favism.

Possibly other so far unexplained hereditary hæmolytic disorders may prove to be due to enzyme defects rather than to allergy or undefined immunological abnormalities. Thus at the recent European conference in London Dr. T. A. J. PRANKERD pointed out that an abnormality of glycolysis has been detected in the red blood-cells in hereditary spherocytosis, and a defect of phosphoglyceromutase has been found in the red cells of a family with the congenital non-spherocytic hæmolytic anæmia described by CROSBY.[41] Such investigations are so far in the early stages. But the Heinz-body test is easy to carry out, and the glutathione-stability test is feasible in any biochemical laboratory; and these tests should clearly be applied in patients with drug-induced hæmolytic anæmia or unidentified hæmolytic anæmia. The workers who began to investigate once again the oddities of the hæmolytic anæmia induced by primaquine can hardly have anticipated that they would end by providing an explanation of favism. There are still many curious facts to be explained about these anæmias, but these researches have notably advanced our understanding of them.

Dental Drills

THE earliest dental drills were based on either the jeweller's bow drill or else the Archimedean drill, which resembled those used in fretwork. The first power-driven drill was invented by G. F. HARRINGTON, who in 1864 patented a clockwork device which would run for two minutes on one winding.[42] The treadle-driven foot engine was introduced by MORRISON in 1870–71. An electrically driven drill had been invented by G. F. GREEN in the 1850s [43]; but this seems to have been little used. In 1868 GREEN introduced a pneumatic engine in which the drill was "propelled by a certain mechanism" contained in the handpiece. The first practical electric engine is supposed to have been made by the firm of Siemens-Schuckert, but the foot engine continued in use well into the 1920s.

Nearly forty years ago it was decided on theoretical grounds that the optimum cutting speed was in the neighbourhood of 300,000 revolutions per minute (r.p.m.) for a 1 mm. ($^1/_{25}$ in.) diameter bur or carborundum point; but no apparatus operated at such a speed, which is the equivalent of a linear speed of 12–15 metres (37–46 feet) per second. Until about 1943, when diamond cutting instruments were introduced, the

35. Beutler, E., Dern, R. J., Flanagan, C. L., Alving, A. S. *ibid.* 1957, **49**, 84.
36. Grunert, R. R., Phillips, P. H. *Arch. Biochem.* 1951, **30**, 217.
37. Beutler, E., Robson, M., Buttenweiser, E. *J. clin. Invest.* 1957, **36**, 617.
38. Sansone, G., Segni, G. *Boll. Soc. ital. Biol. sper.* 1956, **32**, 456; *ibid.* 1958, **35**, 327.
39. Szeinberg, A., Sheba, C., Hirshorn, N., Bodonyi, E. *Blood*, 1957, **12**, 603.
40. Childs, B., Zinkham, W., Browne, E. A., Kimbro, E. L., Torbert, J. V. *Bull. Johns Hopk. Hosp.* 1958, **102**, 21.
41. Crosby, W. H. *Blood*, 1950, **5**, 233.
42. Lufkin, A. W. A History of Dentistry; p. 275. London, 1948.
43. Taylor, J. A. A History of Dentistry; p. 135. Philadelphia, 1922.

maximum speed of most dental engines was about 4000 r.p.m. Tungsten-carbide burs came into production soon afterwards, and they, too, were found to cut better at higher speeds. WALSH and SYMMONS[44] reported that high rotational speeds reduced unpleasant vibration; and this observation was confirmed by INGRAHAM and TANNER,[45] who also noticed that tension, and consequently fatigue, for both operator and patient diminished at speeds over 6000 r.p.m. WALSH and SYMMONS[46] found that the most unpleasant vibrations were those generated at rotational speeds between 6600 and 9500 r.p.m. There is little advantage in increasing speeds from 26,000 to 45,000 r.p.m.; but at speeds from 45,000 to 100,000 r.p.m. there is a spectacular increase in cutting efficiency, which becomes twenty to thirty times that at 4000 r.p.m.[47] The cutting rate of an ordinary steel bur continues to increase with speeds up to 10,000 r.p.m. or thereabouts; diamond instruments perform best at 60,000–80,000 r.p.m.; while the cutting power of tungsten-carbide burs continues to increase with speed up to the maximum at present obtainable. In 1953 NELSEN et al.[48] described a 61,000 r.p.m. hydraulic turbine handpiece, and two years later MCEWEN[49] described a belt-driven handpiece which attained a rotational speed of 200,000 r.p.m.; at this speed the vibration frequencies were beyond the threshold of perception, and the cutting efficiency was far greater than any previously attained. Air-turbine instruments were developed in 1956; these operate at rotational speeds of 200,000–300,000 r.p.m., and use small-diameter diamond or tungsten-carbide cutting tools. Cavity preparation by a carbon-dioxide-propelled jet of aluminium oxide ("airbrasive" technique) and ultrasonic vibratory drills have been tried, but neither method has become popular.

At high speeds, because only a light touch is needed to guide the bur, fatigue in the operator is lessened; and, with the almost fortyfold reduction in the amplitude of vibrations transmitted to the tooth, the whole procedure is much less trying for the patient. This in itself encourages better dentistry, and often a great deal more can be done without recourse to local analgesia. High-speed cutting, though more painful than the abrasive jet, which is the best-tolerated method of all, is nevertheless far more acceptable to the patient than conventional speeds.[50] But what of the risks? The dental pulp may be injured during the preparation of the smallest cavity because of its susceptibility to both thermal and pressure changes. Fortunately this damage is usually only temporary; but the higher the cutting speed and the deeper the cavity, the more lasting is it likely to be. Since the introduction of "threshold" high speeds[50] (10,000–18,000 r.p.m.) it has become usual to cool the tooth with either a jet or a spray of water during cutting. The importance of adequate cooling has been shown by VALE,[51] who measured the temperature rise in the pulp chamber of an extracted tooth. Using a diamond instrument at 3500 r.p.m., the temperature in the pulp chamber rose to 21°C above ambient; with water cooling, the rise was only 4°C. A tungsten-carbide bur rotating at 17,000 r.p.m. caused a temperature rise of 40°C, whereas with spray cooling it was only 9°C. An air turbine with a diamond instrument, using air cooling alone, produced a temperature rise of 16°C, compared with zero when a water jet was used. Some operators (and patients) have remarked on a smell of burning which often accompanies cutting: in some instances incandescence of the enamel has been noted. Whether this is just a surface effect, as is suggested by measurements of pulp-chamber temperature, or whether enough heat is generated to injure the pulp is uncertain; but a sandpaper disc rotating at 4000–5000 r.p.m. can produce the same smell without any complaint from the patient. Air turbines are not suitable for use with large-diameter cutting instruments—the linear speed of a cutting particle on a disc is too high, and the torque of the turbine too low. Damage to the cells of the pulp[51] is a disturbing feature of high-speed cutting. Cell disorganisation is known to develop at frequencies in the neighbourhood of 1·5 megacycles (10^6 cycles) a second, and possibly an air turbine running at 250,000 r.p.m. could generate harmonics at this frequency. Further research is needed into this point, and into the occasional disintegration of large portions of enamel: probably this is due to microscopic flaws in the enamel, or else to the tooth coming into resonance with the natural frequency of the cutting instrument or some harmonic of it.

Even its most enthusiastic advocates cannot deny that the air turbine is noisy, and that its high-pitched whine carries some distance. Surprisingly, the patient is usually the last person to complain of this[50]; airborne noises apparently cause less distress than those conducted through bone. KILPATRICK[50] suggests that the surgery be lined with acoustic tiles, and music played through insert-type earphones to soothe the patient. GARDNER and LICKLIDER[52] have recommended the use, besides music, of a random noise, consisting of a strong, low-frequency component combined with a weaker and higher-frequency one. Fear has been expressed that continual exposure to the high-pitched note of the air turbine may injure the ears of the operator—though no such injury has yet been observed. One manufacturer has reduced the noise by returning most of the exhaust air to the cabinet of the machine. Because of the high frequencies involved, a very small built-in silencer near the rotor of the turbine should eliminate much of the more unpleasant noise, but this does not seem to have been tried. The small ball races in the handpiece contribute a fair amount of mechanical noise, and silencing these presents greater difficulties. Disquiet has also been felt at the force with which particles of tooth substance and pieces of old filling material are propelled into the air by the blast of the turbine exhaust. For the patient this is unlikely to be a serious hazard; but the

44. Walsh, J. P., Symmons, H. F. *N.Z. dent. J.* 1949, **43**, 106.
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49. McEwen, R. A. *N.Y. J. Dent.* 1955, **21**, 475.
50. Kilpatrick, H. C. High Speed and Ultra-speed in Dentistry; p. 261. Philadelphia, 1959.
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52. Gardner, W. J., Licklider, J. C. R. Cited in *New Scientist*, 1959, **5**, 164.

operator might be well advised to wear some form of mask. An aspirator, more efficient than the usual water-operated saliva ejector, is essential; high-velocity suction apparatus is already on the market in the United States.[50] A further hazard concerns the oil which is entrained with the air-supply to lubricate the turbine. The amount of oil used is small (15–30 drops a minute), but it is disturbing to see that one turbine is advertised as using liquid paraffin: the use of vegetable oils might be attended by less risk. There have been rumours of turbines disintegrating, but no instances of this have yet been published, and, in any event, the head of the hand-piece would probably be strong enough to contain the fragments.

Whatever its disadvantages, the high-speed drill is a notable technical advance. It will probably never supplant altogether the conventional electric engine; but when it is used it will make cavity preparation less tiring for the operator and less unpleasant for the patient.

Annotations

WHAT TO EXPECT FROM OUR BABIES

IT may come as a surprise to many that hitherto there have been no accepted weight standards for infants in the first year of life according to birth-weights. Without exact information it has seemed reasonable to suppose that most of the smaller infants at birth would at older ages remain at the lower end of the normal weight-range; but this is disproved by Levin et al. in a study, published by the Medical Research Council,[1] of 521 healthy full-term and 223 premature London infants.

The figures for full-term infants agree closely with those already defined by workers in this country and the U.S.A. Greater interest attaches to the weight records of the premature infants, for these show the overriding influence of an inborn pattern of body size towards which growth proceeds, regardless of accidents such as gestational age at birth. Thus, Levin et al. find that the mean rate of weight-gain of premature infants was equal to that of infants of comparable age from conception who had remained in utero until term. A similar association between gestational age and mean gain in weight during the early months was found in the smaller babies compared with the larger babies with weights above $5^1/_2$ lb. at birth (all of whom are traditionally regarded as full-term), the smaller infants having the greater mean increments of weight in their first year. In fact, at the end of this time there was a difference of only 10 oz. between the mean weights of male infants with birth-weights of 6–7 lb. and of 9–10 lb.

A physiological standard of growth based on gestational age was suggested by previous assessments of fœtal gain in the later months in utero [2 3]; and this was put to the test on a small scale by Young et al.[4] There is now little doubt that the standard weight curves for full-term infants can be applied to premature infants by correcting for their age from conception, gauged by birth-weight. For example, using Levin's standard curve, the correcting factor for infants weighing $2^1/_2$ lb. at birth is $2^1/_2$ months; so a 5-month-old infant with this birth-weight should be compared with the full-term standards of 5 less $2^1/_2$—i.e., $2^1/_2$—months. On the same basis healthy infants who have a higher than average birth-weight should be regarded as postmature.

The weight gains of the premature infants in the series were high in comparison with published figures,[5] reflecting a successful plan of nutrition. Most were artificially fed partly or completely, but all the smaller ones received human milk in the first one or two weeks until feeding habits were well established, and a small group under $4^1/_2$ lb. were fed on breast-milk alone until they were 8 weeks of age. Between 2 and 8 weeks of age the weekly mean gains in weight of this group were lower than those of comparable infants given cow's milk mixtures at the same stage—a difference that has been previously recorded. The lower gains can be attributed to the lower protein content of human milk, which has been calculated as insufficient to allow for the "normal" high rate of growth relative to body size between the 28th and 40th weeks from conception. In contrast, the breast-fed and artificially fed full-term infants up to 5 months of age gained weight at equal rates, which is to be expected from the amount of protein in an ordinary supply of human milk at this time. But, as Levin et al. remark, breast-milk is unlikely to provide a satisfactory protein intake for a wasted full-term infant: with a higher intake his weight might catch up more quickly with that appropriate for his size. On the other hand, it is important to avoid prescribing the usual cow's milk mixtures, with their high protein and electrolyte content, for some infants in whom growth is slow or arrested, such as those with congenital cardiac or renal abnormalities, or those with acute illnesses due to infection (which includes many infants at one time or another before weaning age); otherwise the stress of a high excretory load may precipitate dehydration crises and electrolyte imbalance [6]—a point that is often overlooked in comparing the merits of artificial and of breast feeding. Breast-milk is thus the best food for the infant born at term: in health this enables him to grow at an optimal rate, and in disease it enables him to withstand phases of stress with the least possible disturbance of his internal milieu.

The initial motive in collecting the clinical records of the infants was to provide a background for serum-protein studies. These, too, were of special interest in relation to prematurity. Analysis showed that, the lower the birth-weight, the lower the serum protein, albumin, and globulin levels at all ages from birth to 3–5 months. Grouping the infants by age from conception, Levin et al. showed that the serum-protein level corresponds with the maturity of the infant. A single curve for infants of all birth-weights shows the changes with age from 28 to 92 weeks from conception. This is a new approach which gives a clearer understanding of the changes with age; and now the significance of other variables may be more accurately assessed. Several of these were investigated but were found to be without effect on the serum-protein levels; changes in weight were a more sensitive index of nutritional sufficiency.

1. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1959, no. 296. Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants, Full Term and Premature. By B. Levin, Helen M. M. Mackay, Catherine A. Neill, V. G. Oberholzer, and T. P. Whitehead. H.M. Stationery Office. Pp. 154. 16*s*.
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3. Huggett, A. St. G. *Brit. med. Bull.* 1946, **4**, 196.
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The report also contains sections on hæmoglobin levels, on serum-non-protein-nitrogen levels in relation to age and diet, and on γ-globulin levels in relation to age. This valuable collection of data will be a useful source of standards for all concerned with the development of infants. It will undoubtedly promote a more rational approach to the assessment of setbacks to growth due to either disease or dietary insufficiency.

GASTRIC OUTLINE AND MOTILITY

THE normal stomach shows a wide range of outline and motility; but the descriptive terms applied to the outline—cup-and-spill, cascade, steer-horn, sthenic, and so on—and expressions such as hyperperistalsis and gastrospasm applied to its motility do not encourage understanding of why any one patient's stomach is as it is.

The radiographic outline of the gastric cavity is a model of the mucosal outline, which changes from moment to moment as a result of movement of the mucosal layer on the innermost muscular coat; grosser changes in outline result from contraction of the muscle coats. In the longitudinal part of the stomach contraction of the oblique muscle-fibres which form the innermost muscular layer produces a coarsely notched appearance of the greater curvature. This feature is often accentuated in the presence of ulceration, and it terminates abruptly where the oblique fibres are replaced by the circular fibres as the innermost muscle layer, at the transition from the longitudinal to the transverse part of the stomach.

In the normal stomach peristalsis begins near the cardia, and wave follows wave at a rate of about nine contractions a minute. Though stimulation of vagal cholinergic fibres excites peristalsis, and stimulation of adrenergic sympathetic fibres decreases the rate, the pacemaker is probably spontaneous muscular contraction, since excised strips of muscle from the cardia contract at roughly the same frequency as the normal stomach. Strong emotional stimuli of anger and anxiety increase the rate and depth of contraction,[1] and fear can temporarily interrupt peristalsis.[2] The longitudinal and transverse portions of the stomach probably have inherently different contractile patterns. By sectioning cats' stomachs at the junction of the longitudinal and transverse portions Borchers [3] showed that the frequencies of gastric contractions above and below the line of section were quite independent of each other: in the longitudinal part four waves of contraction occurred in the same time that two or three occurred in the transverse portion below the section. Borchers also showed that section nearer the pylorus was followed by tonic contraction of the pyloric antrum. Gastric emptying is not the only factor influencing peristaltic activity. The physical state and the nature of the gastric contents are also important; fluid contents pass out rapidly, and food containing a high proportion of fat is retained longest.[4]

Lilja [5] has related the appearances during radiological examination with the structure and behaviour of the healthy and the ulcerated stomach. The appearances in peptic ulceration are well recognised. Chronic ulceration in the upper and middle thirds of the stomach is associated with shortening of the lesser curvature and increased indentation of the greater curvature in the longitudinal part of the stomach; an ulcer on the upper third of the posterior wall of the longitudinal part with a cascade type of stomach; a penetrating ulcer at the angulus with impaired emptying and dilatation and poor peristalsis in the transverse portion of the stomach; and ulceration in the roof of the transverse portion with concentric antral contraction. Lilja suggests that in ulceration of the longitudinal part of the stomach spasmodic contraction of the inner coat of oblique muscle-fibres is later followed by fibrosis, and that in ulceration at the angulus there is peristaltic conduction blockage. He suggests, too, that angulus ulceration may destroy a specialised motor centre situated there.

The influence of gastritis on the appearances of the stomach outline is debatable. Henning [6] stated that broad and thick folds in the stomach were often seen radiologically in a stomach that was histologically normal, and that even with total atrophy of the mucosal layer the rugæ might appear broad and thick. Increased folding and irregularity in the stomach outline may result from increased gastric tone. Magnus [7] stated that in chronic gastritis a considerable decrease in the number of mucosal glands might be accompanied by a corresponding increase in the areolar tissue in the mucosa, and that accordingly the mucosa itself might not become as thin as it would otherwise be. Magnus regarded the mucosal change in pernicious anæmia as purely atrophic, without any increase in the interstitial tissue. This true atrophy is limited to the longitudinal part of the stomach and terminates abruptly; the mucosa in the transverse portion of the stomach is either normal or the seat of non-specific gastritis. The atrophic changes in the longitudinal part of the stomach in pernicious anæmia involve all coats of the stomach, and the naked-eye appearance is striking. Pitman and Laws [8] suspect pernicious anæmia when they observe radiologically a smooth fundus devoid of normal folding, a smooth and rather uniformly tubular longitudinal gastric segment with poor peristaltic contraction, and fine " crushed tissue-paper " rugæ in the empty longitudinal part of the stomach with normal rugal pattern in the transverse part. These findings are complementary to Magnus' account of the histological appearance. In this instance the radiological diagnosis of gastritis seems to have passed beyond the stage of mere fancy.

The work of Lilja and others shows that the connection between lesions of the mucosa and the substrate of muscular tissue of the stomach wall is closer and more extensive, even in non-neoplastic conditions, than many of us had thought likely.

ALCOHOL AND DRIVING ABILITY

A NEW Medical Research Council memorandum [9] describes experiments designed to investigate the effects of small doses of alcohol on a skill resembling car driving.[10] Inquiries were also made into individual differences in response to alcohol, particularly in relation to personality ratings, and various methods of estimating blood-alcohol were compared.

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10. See *Lancet*, 1959, ii, 51.

The subjects of the experiments were 35 male and 5 female members of the staff of the Road Research Laboratory; 1 was aged 58, and the others were between 23 and 40. All were of good intelligence, and most were occasional or moderate drinkers. All held driving licences, but they had had varied driving experience. The skill tested was that of " driving " a fixed car-like apparatus (a Miles motor-driving trainer) along what appeared to the subject to be a winding tree-fringed road. During a 30-minute practice run, blood samples were drawn to familiarise the subject with this procedure; and personality testing was performed the same day. A week later each subject began a series of 5 regular weekly 2-hour " driving tests ", after taking one of five standard drinks: four consisted of a 20% solution of ethyl alcohol with an alcohol content corresponding to 0·20, 0·35, 0·50, and 0·65 g. per kg. body-weight per subject; and the fifth was an alcohol-free " placebo ". All were heavily flavoured with peppermint and ginger so that it was impossible to detect whether alcohol was present or in what amount. During the test run an automatic record was made of " speeds ", tracking errors (i.e., variations from a steady course), kerb bumpings, steering-wheel and accelerator movements, brake applications, and gear changes. Save for kerb bumps, which were signalled by a loud buzzer, the driver was not informed of his performance during the tests. Each test was interrupted every half-hour when samples of blood (by pinprick), urine, and occasionally breath were taken for alcohol estimations.

The largest dose of alcohol was equivalent to about 3 pints of beer or 5 fluid ounces of whisky, for a man of average weight, and after each alcoholic drink the blood-alcohol rose sharply to a peak in 30–60 minutes. Urinary alcohol rose more slowly and to a higher peak than in blood. Tests on breath samples showed that, with the 'Drunkometer' and 'Breathalyser' calibrated to give the corresponding blood-alcohol values, there was good agreement with directly measured blood-alcohol figures: similar tests with the 'Alcometer' were satisfactory at first but then became unreliable, possibly because moisture accumulated in the apparatus.

The results showed a definite decline in skill with increasing blood-alcohol; a deterioration of about 12% in driving accuracy was associated with a blood-alcohol of about 80 mg. per 100 ml. Drivers influenced by alcohol tended to steer less consistently and to deviate more and more from the nearside kerb: swerves away from the near-side kerb were less quickly corrected, but any tendency to steer into this kerb was more rapidly controlled. These responses resemble those of fatigued persons, and they may represent increasing tolerance to error—an increase in the " indifference range "—which may explain the subjective impression of improved precision when in fact skill is diminishing. After alcohol, extroverts drove on with maintained speed and many errors; introverts, apparently anxious to demonstrate their efficiency and trying to overcome the effects of alcohol, either slowed down appreciably without necessarily improving performance, or else speeded up, usually with little increase in errors.

The time lapse after drinking did not materially affect performance; the effect of alcohol, once apparent, persisted during the 2 hours of the test, possibly because the blood-alcohol did not fall appreciably in that time. Age, sex, drinking habits, and driving experience showed no relation to individual differences in response to alcohol. In the group as a whole, performance was affected by the lowest dose of alcohol—corresponding to a blood-alcohol of only 20–30 mg. per 100 ml.—and it seems clear from this carefully designed and conducted experiment that blood-alcohol in the smallest quantities detectable by existing instruments may cause measurable deterioration in skill.

INVOLUTIONAL MELANCHOLIA

IT has long been agreed that manic-depressive psychosis may start late in life, but whether there is another condition—" involutional melancholia "—is disputed. The symptoms are said to differ from those of other depressive illnesses. Anxiety, manifested by severe restlessness and agitation, is held to be conspicuous; retardation is usually not prominent; and there is often a rich development of delusions (frequently bizarre and hypochondriacal) centred on feelings of guilt.[1] The onset is usually insidious and the previous personality somewhat obsessional. Cases of this kind are certainly to be found, but often the picture does not accord closely with this description. Perhaps, as Lewis [2] suggested, the rather different manifestations of depression in later life can be explained by the influence of age itself.

The evidence for separating involutional from manic-depressive cases is largely genetic. Thus Kallman [3] found that the risk of schizophrenia in first-degree relatives of involutional melancholics was 6%—significantly greater than in the general population—whereas the incidence in the relatives of manic-depressives was no greater than the average. But Kallman's concept of schizophrenia is wider than that usually accepted here, and doubt has been cast on his findings. Kay,[4] for example, in his Stockholm study found an incidence of 2·5–4·2%; but of his 10 probands with schizophrenic relatives the majority had atypical psychoses, and in 3 there had been doubts about classification. Also, of the 11 schizophrenic relatives the diagnosis was regarded as doubtful in 4. He concluded that " the risk for schizophrenia among the relatives . . . is not definitely increased ". Stenstedt,[5] in a particularly careful study, detected no increase of schizophrenia among the relatives of 307 involutional melancholics. Affective illness, however, appeared in about 6% of the first-degree relatives, compared with some 3% in the general population and 12% among similar relatives of patients with manic-depressive psychosis.[6] In his cases, as in those of Kay, there were more with prominent exogenous factors than is usual in a group of younger depressed patients. Exogenous factors were particularly prominent in the oldest age-groups, where the incidence of affective illness in relatives was also less. Excluding cases with presumed exogenous factors, the incidence in relatives was 9·4%—not dissimilar to the figure in cases of manic-depressive psychosis. It seems that the earlier the onset the more " endogenous " the illness and the greater the genetic predisposition.

Perhaps " involutional melancholia " embraces a heterogeneous group of disorders, including manic-depression of late onset and simple depression with predominant exogenous factors. There seems to be little justification for retaining it as a separate diagnostic entity.

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Points of View

HÆMATOLOGY IN BRITISH HOSPITALS

PRESENT CONDITIONS AND FUTURE POSSIBILITIES

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HÆMATOLOGY is a relatively new specialty, and in this country hæmatologists were a rare species before the late war. Till then, in England at least, the investigation of blood diseases was carried out in most hospitals in a corner of the general pathological laboratory by the hospital clinical pathologist or his assistant. It seems hardly credible that in 1936 when I was resident pathologist in a London teaching hospital my duties, which were not confined to hæmatology, included carrying out unaided all the blood-counts made on inpatients and outpatients, including collecting the blood, and giving blood-transfusions, as well as collecting blood from the donors and cross-matching it. None of the small staff of technicians helped with the blood-counts.

In the past twenty years or so knowledge of the blood diseases has advanced in many directions and many new and complicated techniques have been introduced; even the vocabulary of hæmatology has been transformed. Vitamin B_{12}, folic acid, Christmas disease, hæmoglobin-S, the Rh blood-groups, Coombs' test, and 6-mercaptopurine were all unknown in the late 'thirties. Each of these familiar terms is now surrounded by a vast literature; and the megaloblastic anæmias, the hæmorrhagic disorders, the abnormal hæmoglobins, blood-group serology, and the chemotherapy of leukæmia have all become subspecialties of hæmatology, each large enough for lifelong study. These remarkable developments pose problems of organisation and administration which I feel have not received the attention they deserve. The particular problem with which I am concerned is how best a hæmatologist and the hæmatological department (if there is one) can be fitted into the organisation of hospital medicine.

PRESENT PATTERN

Today a hæmatologist is almost always a pathologist who has spent nearly all his professional life in a laboratory. He may spend all his time on the investigation of patients with blood diseases, or he may do this in addition to undertaking another branch of clinical pathology—e.g., bacteriology or chemical pathology. More and more, however, I believe the trend in the larger laboratories is towards appointing a pathologist primarily to do hæmatology and to help with other branches only in emergencies or when another member of the staff of the pathological department is on holiday. He probably also supervises the transfusion services of the hospital. In large institutions, and particularly in the teaching hospitals, the laboratory hæmatologist, as I shall call him, often has his own staff of medically qualified assistants.

This pattern is, I believe, almost universal in England —even in teaching hospitals where the medical unit also specialises in hæmatological work and has its own laboratory and staff and carries out hæmatological investigations on the unit's patients. Even then the hæmatological work of the rest of the hospital is usually done by a hæmatologist in the hospital's clinical-pathology laboratory. In Scotland, though there are professorial medical units whose chief concern is hæmatology, hæmatological investigations have in the past usually been carried out in clinical side-rooms by the staff of the physicians in charge of wards, with occasional consultation with or reference to a colleague. This traditional procedure can hardly be expected to keep abreast with the demands of present-day hæmatological techniques, and in some hospitals at least other arrangements are being made.

DAY-TO-DAY DUTIES

The scope of a laboratory hæmatologist's work varies with local circumstances; but, leaving aside the possibilities of teaching and research, his work falls into two main categories.

First, he has to organise and supervise for his hospital a routine or screening service from which the medical staff of all departments can obtain elementary but expertly interpreted hæmatological data on their patients—e.g., hæmoglobin, leucocyte-counts, prothrombin-times, reports on blood-films, blood-grouping and cross-matching tests, and tests for antibodies in antenatal patients. All this work, more often than not, gives normal results and is usually left to the technical staff. It is time-consuming, exacting, and wearisome, but necessary, and it should be supervised by a hæmatologist. Its centralisation in a single laboratory enables this to be done and makes possible the early diagnosis of blood diseases. Shortage of staff often makes it difficult for the hæmatologist to give as good a service as he would like to, and here clinicians can help tremendously by leaving the decision as to what should be done and what need not be done in a particular case to the hæmatologist's judgment.

The second, and more exciting, side of a laboratory hæmatologist's work is the detailed investigation of patients whose blood is abnormal. In this he can often be of real help to his clinical colleagues, for it is almost impossible to diagnose a blood disease exactly without the aid of laboratory tests and experience in interpreting the findings. The central position of his laboratory (this unfortunately is often not geographically true), with all the patients in the hospital potentially a source of hæmatological problems, gives the laboratory hæmatologist remarkable opportunities for the study of a wide range of blood diseases at all stages in their evolution. In this way he rapidly becomes experienced in the investigation of obscure conditions and in advising on the treatment of blood diseases generally; particularly is this true of the management of patients with megaloblastic anæmia, leukæmia, hæmophilia, and hæmolytic anæmia. Recognition of this has led to the hæmatologist sharing more and more in the patient's care, and to the physician in charge often passing over to him the virtual management of the patient's hæmatological treatment and follow-up. This arrangement is a happy one for the laboratory hæmatologist and the physician as well as for the patient.

Finally, the hospital clinical-pathology laboratory may provide a general-practitioner diagnostic service. If so, an important part of this work is hæmatological. I do not deny that this is necessary, but in my view a proper provision of space and staff should be allotted for this work.

RESEARCH

It is every doctor's clear duty to contribute to knowledge of the branch of medicine in which he is working, and facilities for this and encouragement should, ideally, always be available. This is of course easier in the teaching hospitals than elsewhere, and it is unrealistic to suppose that a hæmatologist working in the clinical-

pathology laboratory of a busy non-teaching hospital is likely to have time for research. In most instances he has barely time to do the basic essentials of his work. As for reading, trying fancy techniques, or experimentation, these are impossible. But for the fortunate few who have the time, or make the time, the relation between clinician and hæmatologist is important; for the type of research possible to a hæmatologist almost always involves multiple tests on patients, careful follow-up studies, or assessment of responses to treatment. It seems right to me that the man who supervises the routine hæmatological work should have the opportunity of carrying out research in the same field, alone or in collaboration with his clinical colleagues. I regard it as an unhappy state of affairs if the laboratory hæmatologist is prevented from carrying out research because he has not easy access to patients.

It is unfair to the hæmatologist if research on blood diseases is carried out by the clinical staff (who use the hæmatologist's basic data) because they have the time and the necessary apparatus as well as complete access to the patients, while the hæmatologist (who may know more about the problem) is left with his insufficient staff to cope with the routine demands of the whole hospital. Under these circumstances a post in the hospital clinical-pathology laboratory is hardly likely to attract first-class applicants.

SUGGESTIONS FOR THE FUTURE

I have tried to sketch briefly some of the problems surrounding the hæmatologist and his laboratory. How about the patient? He clearly needs to be looked after by a physician who can view him as a whole as well as having his blood disease accurately diagnosed. The effects of a blood disease are seldom confined to the blood; almost every system in the body, from the brain to the heart, gastrointestinal tract, kidneys, and skin may be involved. For this reason, I have never subscribed to the idea that the laboratory hæmatologist should aim at having beds of his own and complete charge of patients. But how can the laboratory hæmatologist's knowledge and experience and his natural desire for some control over the investigations and treatment of patients be reconciled with the undoubted right of clinicians to have full charge of and responsibility for patients in their care? This is the crux of the problem, and I believe it exercises to a greater or lesser degree the mind of every laboratory hæmatologist.

My solution (which some may consider a pipe-dream, wild and impracticable) is in essence that hæmatology should be recognised as a subject worthy of a department to itself, and that the department, while retaining its administrative links with the department of pathology or the clinical-pathology laboratory, should have a definite link with the medical side of the hospital. The staff of my ideal department of hæmatology would be:

1. The laboratory hæmatologist (director of hæmatological laboratory). He should be primarily a clinical pathologist, who has had a good basic training in general pathology, but who has spent most of his professional life working at hæmatology. He should not be a clinician, though the more he knows of clinical medicine the better.

2. According to the size of the hospital, whether it is a teaching hospital or not, and the character of the teaching, the director should have one or more colleagues of consultant grade. One of these should be a consultant physician holding a joint appointment in the departments of medicine and hæmatology. He should have beds over which he has full charge, and these beds should be reserved for hæmatological problems. He might perhaps have a few general medical beds also. The hæmatological physician (as I shall call him), with the laboratory hæmatologist and other members of the department of hæmatology, would act as consultants, if asked, for hæmatological patients throughout the rest of the hospital. Such an appointment would provide openings for young physicians with a deep interest in hæmatology but who wish to remain physicians and to have contact with and responsibility for patients with blood diseases. At present opportunities for such physicians are almost non-existent in this country. Their training should have been as physicians, and they need not necessarily have had any previous experience of general pathology in order to get appointed, though they would find this an advantage. They might well develop research interests in such subjects as chemotherapy applied to blood diseases.

3. Again according to the size of the organisation, there should be one or more registrars, at least one of whom should be a trainee physician working partly in the laboratory and partly in the wards.

4. It would be desirable to have one of the hospital radiotherapists specialise in the application of radiotherapy and radioactive isotopes to hæmatological diseases. He might well have some status in the department of hæmatology.

5. An adequate staff of technicians, secretaries, laboratory clerks, &c. I believe that most laboratories are understaffed.

The size of the hæmatology department will naturally vary greatly from hospital to hospital. Nevertheless, the principle of a close link between hæmatology and medicine could, I think, be applied almost anywhere. The duties of the department would broadly be (the order is not meant to have significance):

The provision of a routine, or screening, diagnostic hæmatological service for the whole hospital.

The investigation and exact diagnosis of cases of blood diseases throughout the hospital; the supervision of treatment of inpatients with blood diseases in the department's beds, and the provision of an advisory service for the rest of the hospital.

Organisation of follow-up clinics for blood diseases, including megaloblastic anæmia, hæmophilia, leukæmia, and polycythæmia clinics, as well as joint clinics, with the appropriate clinical staff, for blood abnormalities which are commonly associated with another disease—e.g., anæmia and disease of the gastrointestinal tract.

The provision of a blood-transfusion service for the hospital, excluding giving blood and bleeding donors.

The conduct of research and teaching.

". . . The good husband is now the domesticated husband—the man who, when he has finished his work at the factory or the office, spends his evenings and his weekends not with his workmates but at home with his family, enjoying common fireside relaxations with them, or else 'pottering' round the house maintaining or improving its comfort and appearance. Once he sought to escape from the crowded shabbiness of his home to the warmth and conviviality of 'pubs' or the club rooms of voluntary associations, and inevitably in the process he developed social interests and wider loyalties. But now . . . the new man stays at home, and he is likely to find burdensome and repugnant any activities or interests that force him to leave the family circle and to forgo part of his domestic privacy and comfort. . . . If his outside contacts are weakened and reduced in favour of his home ties, this will affect all his group relations. Reduced attendance at trades-union meetings, at Friendly Societies and other club activities, at political discussions, and at all forms of outdoor mass entertainment and activity will inevitably affect his attitudes towards the social institutions they serve. Thanks to television and radio he is, as a spectator and listener, able to sit at home and participate in these activities to a much greater extent than ever before. But the participation is that of a detached, isolated observer served by technicians who are able to multiply his eyes and his ears, and by commentators able to develop his professional critical abilities."—MARK ABRAMS, *Listener*, Nov. 26, 1959, p. 915.

Special Articles

THE COST OF DRUG TREATMENT

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MAN's addiction to pills and potions is as old as history, but until recently reliable evidence has been lacking about such changes as may have occurred over the years in the relative proportion of our national resources which has been devoted to the provision of drugs.

Official anxiety about such expenditure dates from the time when this first became a charge on public funds, and has become more vocal with the much-publicised rise in the national drug bill from £31 million to £62 million which took place between 1949 and 1958. For the first time this change in the method of payment for medicines has permitted an assessment of their national consumption in terms of money, and has activated the concern which is always evident in matters of public accountability: the equanimity with which a comparable dissipation of national resources was regarded while the transactions remained in private hands is a familiar phenomenon.

The discovery by politicians that a comprehensive health service—even though it is no longer literally " free and open to all "—is an even more expensive business than they had anticipated has provoked a crescendo of Ministerial inquiries and exhortations which conveys a general implication that either the rapacity of patients or the complaisant negligence of doctors, or both, must be held responsible for a considerable proportion of the rising costs. The administrators' failure to evolve a less expensive system of supplying the drug to the patient, and the politician's responsibility for inflation, are less frequently inculpated in public discussion, although in fact allowance for the falling value of the pound during the decade in question reduces the " real " increase in the drug bill from 100% to 40%.

Official homilies are couched in general terms, and often deal with figures so astronomical as to be meaningless to the average doctor. The present paper is based on a clinical lecture to medical students, directing their attention to the average weekly cost of some widely used forms of medical treatment with drugs as they are dispensed in general practice. This seemed a simple enough undertaking, but we soon discovered that the problem was both more complex and more intriguing than would appear at first sight. Finding that our ignorance of the subject was shared by many of our colleagues we considered the facts worthy of wider circulation.

Method of Costing Prescriptions

The total cost of a general practitioner's prescription is the sum of four separate items: (1) the basic cost of the drug; (2) the " on-cost ", which is 25% of the basic cost, and represents the permitted margin of gross profit to the pharmacist; (3) a container allowance of about 1½*d.*; and (4) a dispensing fee of at least 1*s.* 2*d.* for the pharmacist's professional services. Under present conditions the patient contributes 1*s.* to the cost of each prescription. It will be seen that the " basic cost of the drug to the N.H.S." may be a very different matter from the actual charge on the Exchequer.

Indeed, the system has some curious results. The " basic cost " of half a grain of phenobarbitone three times a day for a week is 1*d.* The " on-cost " raises this to 1¼*d.* and the container allowance to 2¾*d.* A dispensing charge of 1*s.* 2*d.* recompenses the pharmacist for the professional skill involved in dispensing the prescription. The total cost of the pennyworth of phenobarbitone is therefore raised by more than 1600% to 1*s.* 4¾*d.* The example of terramycin shows the working of the system in a different way. The basic cost of one gramme of this drug daily for seven days is £1 19*s.* 8*d.* On this the pharmacist is allowed a profit of 9*s.* 11*d.* and a dispensing fee of 1*s.* 2*d.*, raising the total cost of a week's supply of the drug to £2 10*s.* 10½*d.*

Examples

The weekly cost of treatment with some familiar drugs in average doses as prescribed by the general practitioner is set out below to the nearest penny. The figures relate to prices prevailing in July, 1959, and have been averaged to allow for occasional variable factors. The " prescription charge " of 1*s.* is excluded from consideration here; but it is universally applicable, and has the effect of reducing the cost to the Exchequer by 1*s.* in every instance.

CARDIOVASCULAR DISEASE

The treatment of *heart-disease* is generally inexpensive. The average weekly cost of digitalisation varies from 1*s.* 5*d.* (digitalis leaf *N.F.*) through 1*s.* 6*d.* (tincture) and 1*s.* 9*d.* (digoxin) to 2*s.* 0*d.* (digitoxin). The weekly injection of mersalyl costs 1*s.* 8*d.* (basic cost of the drug is 3½*d.*) but four days of ' Saluric ' costs 5*s.* 8*d.* and a week's supply of hydrochlorothiazide 10*s.* 6*d.*

The long-term medical management of *hypertension* is usually a more expensive business, the average weekly cost of ' Serpasil ' being about 2*s.* 9*d.*, ' Ansolysen ' 6*s.* 3*d.*, ' Apresoline ' 6*s.* 7*d.*, ' Tenormal ' 7*s.* 10*d.*, and ' Inversine ' 8*s.* 3*d.* If pilocarpine is administered simultaneously to control side-effects the cost is raised by another 5*s.* 6*d.* weekly.

The treatment of *angina* costs 1*s.* 5*d.* per week with nitroglycerin, 1*s.* 11*d.* with ' Peritrate ', 2*s.* 5*d.* with ' Mycardol ', and 6*s.* 2*d.* with ' Marsilid '.

With regard to *anticoagulant* treatment, heparin is notoriously expensive (£2 17*s.* 6*d.* for 48 hours), dicoumarol at 3*s.* 2*d.* and ' Dindevan ' at 3*s.* 0*d.* weekly much less so.

NEUROLOGICAL DISORDERS

The cost of treating *epilepsy* varies from 1*s.* 5*d.* weekly (phenobarbitone) through 2*s.* 6*d.* (' Epanutin '), 4*s.* 3*d.* (' Mysoline '), and 5*s.* 6*d.* (' Tridione ') to £1 6*s.* 6*d.* (' Nydrane ').

For the prophylaxis of *migraine*, Gowers' mixture costs 2*s.* 5*d.* weekly, ' Stemetil ' 6*s.* 6*d.* However, the treatment of an individual attack with three tablets of ' Cafergot ' may cost from 1*s.* 6*d.* to 2*s.* 6*d.*, and with ' Migril ' from 2*s.* 1*d.* to 3*s.* 11*d.*, depending on the number of tablets prescribed at a time.

Myasthenia gravis is a fairly expensive illness. In low average dosage of two fifteen-milligramme tablets three times daily ' Prostigmin ' costs 6*s.* 6*d.* weekly, comparable dosage with ' Mestinon ' 15*s.* 3*d.* For parkinsonism ' Artane ' (3*s.* 1*d.*) now costs no more than tincture of stramonium or hyoscine hydrobromide. ' Cogentin ' (6*s.* 2*d.*) is twice as dear, but ' Kemadrin ' (2*s.* 8*d.*) represents one instance where the prescription of a proprietary drug represents an economy.

Wilson's disease costs 3*s.* 4*d.* weekly treated with calcium versenate, 4*s.* 11*d.* with dimercaprol (BAL), and about £15 10*s.* 0*d.* with penicillamine.

INFECTIONS

Sulphonamides are cheap, a week's supply of sulphamezathine costing only 3*s.* 2*d.* The weekly cost of a daily injection of one mega-unit of penicillin is 10*s.*, but oral penicillin V in tablet form in dosage which most would consider no more than adequate for the treatment of a severe infection (one gramme

daily) might cost £1 7*s*. 6*d*. weekly, or £2 19*s*. 7*d*. in suspension. In the latter form, indeed, oral penicillin is probably the most expensive antibiotic in general use, the average weekly cost of the others varying from £1 13*s*. 4*d*. ('Chloromycetin'), to £2 5*s*. 0*d*. (erythromycin), £2 7*s*. 1*d*. (aureomycin and 'Achromycin'), £2 10*s*. 10*d*. (terramycin), and £2 18*s*. 2*d*. (neomycin).

Streptomycin costs 14*s*. 5*d*. weekly and isoniazid only 1*s*. 10*d*., but *p*-aminosalicylic acid (P.A.S.) £1 2*s*. 11*d*.

ENDOCRINE PREPARATIONS

The cost of treatment of *diabetes mellitus* is almost independent of the type of insulin employed. Twenty units of soluble insulin twice daily costs 5*s*. 1*d*. weekly, protamine zinc insulin or globin insulin in comparable dosage 5*s*. 3*d*. A syringe and one packet of needles costs 8*s*. 1*d*. Tolbutamide (5*s*. 10*d*.) is comparable in cost with insulin.

In the treatment of *hypothyroidism*, L-thyroxine (1*s*. 10*d*.) is only slightly dearer than thyroid extract (1*s*. 6*d*.). In Graves' disease a week of methylthiouracil costs 1*s*. 5*d*., a week of 'Neo-mercazole' 4*s*. 0*d*. In the treatment of *Addison's disease* ten grammes of sodium chloride daily costs 2*s*. 7*d*. weekly, fluorohydrocortisone 6*s*. 6*d*.

The comparative costs of various therapeutic routines in *rheumatoid arthritis* are of some interest. Aspirin costs 1*s*. 10*d*. weekly, calcium aspirin 2*s*. 7*d*., 'Paynocil' 6*s*. 0*d*., 'Butazolidin' 8*s*. 7*d*., prednisone 15*s*. 5*d*., and cortisone £1 0*s*. 10*d*.

EMOTIONAL SYMPTOMS

Modern preparations for *sleeplessness* are not expensive. Nightly 'Soneryl' costs 1*s*. 11*d*. weekly, 'Seconal' 2*s*. 1*d*., 'Tuinal' 2*s*. 8*d*., and 'Carbrital' 3*s*. 2*d*.

'Amytal' (2*s*. 0*d*.) remains the cheapest ataractic, 'Largactil' costing 3*s*. 10*d*., 'Oblivon' 4*s*. 0*d*., and 'Equanil' 4*s*. 4*d*.

'Dexedrine' in tablets costs 1*s*. 5*d*., in 'Spansule' form 2*s*. 6*d*. The new antidepressive preparation 'Tofranil' costs 17*s*. 6*d*. weekly for average maintenance dosage.

Discussion

These figures demonstrate the low basic cost of many of the drugs most widely used. It is a remarkable tribute to the efficiency of the pharmaceutical industry that a week's supply of phenobarbitone or digitalis in reliably standardised dosage can be furnished by the industry for a "basic cost" of 1*d*., with dextroamphetamine for 1½*d*., and with thyroid extract for 2*d*. In such instances a distributive cost which may exceed 1500% is startling, while the "on-cost" in the case of the more expensive preparation (e.g., 11*s*. 4½*d*. on seven grammes of neomycin) also makes an appreciable contribution to the final cost of the prescription. In general the cost of distribution adds 50% to the basic cost of the drugs considered above —a figure which suggests that distributive costs may account for one-third of the total national drug bill.

The dispensing fee is intended as remuneration for the pharmacist's professional services in making up the prescription. In the calculations noted above the flat-rate dispensing fee of 1*s*. 2*d*. has been added to the basic cost of the drug, but in fact this is the minimum. The dispensing fee on 42 tablets of phenobarbitone is 1*s*. 2*d*., but on a prescription for 350 tablets it is 4*s*. 0*d*. The compounding of medicines in the pharmacy is steadily declining, and at the present time probably rather more than three-quarters of all National Health Service prescriptions are for tablets the dispensing of which does not call for any high degree of professional skill.

Expensive Drugs

Expensive drugs are of three kinds: first, those which are genuinely expensive to manufacture (e.g., penicillamine); secondly, new drugs in which the costs of development must be recouped by an initially high price (e.g., nydrane); and, thirdly, special preparations of banal remedies (e.g., phenobarbitone in spansule form).

Penicillamine is produced by a complex and expensive chemical process, and it has no use whatever except in the treatment of Wilson's disease. The high cost of the drug covers no more than the expense of manufacture. Its use represents a real advance in the treatment of this distressing disease. It goes far to correct the biochemical anomaly which is at the root of the condition, and may produce considerable symptomatic improvement. It is not a cure and it rarely restores social efficiency. On the other hand its employment may allow home rather than institutional care. It is difficult to see any justification for denying its continued administration to any patient with this disease who obtains unequivocal benefit from it, but at an average annual cost of £750 its prescription cannot but cause the physician some concern.

One special reason for this is that although the day-to-day care of the patient may have passed into the hands of her general practitioner the drug is always distributed from a hospital pharmacy, and the maintenance of two sibs with Wilson's disease may saddle the hospital with an annual expenditure of £1500 or more. The physician knows that no special financial allotment is made in such cases, and that the money must come from an annual Ministerial allowance for running expenses which is regularly thousands of pounds below what the hospital administration has carefully estimated as necessary to provide an efficient service. In fact he knows that the provision of such treatment may reduce the amount of cash available to the hospital for the purchase of such requisites as surgical instruments.

The instance of penicillamine emphasises another anomaly of wider implications. It is cheaper to supply drugs from a hospital dispensary than by means of a general practitioner's prescription dispensed by a private pharmacist. The hospital has the advantage of bulk purchase, there is no "on-cost", and the proportion of the hospital pharmacist's salary which can be related to the service involved in a single prescription is very much less than even the minimum dispensing fee of 1*s*. 2*d*.[1] However, the system of hospital budgeting is such that some hospital administrations have found it necessary to advise their medical staffs to cut down the treatment of outpatients with drugs from the hospital dispensary in favour of the patient's earlier reference back to his general practitioner, even though there are many instances where hospital supervision is a convenient as well as an efficient and economic temporary arrangement. Paradoxically, the hospital, in an attempt to balance its own budget, finds itself obliged to advise a course of action which involves an increased charge on public funds.

Difficulties also arise in relation to the second group of expensive drugs. At a time of unparalleled advance in pharmacology the doctor is subjected to a daily barrage of advertisements for new preparations, many of which are expensive. A few of these find an established place in current therapeutics. For example, artane, introduced as a rather expensive proprietary preparation ten years ago, is now probably the most widely used drug in the treatment of Parkinson's disease and has become slightly cheaper (as well as more convenient and more chemically stable) than the traditional hyoscine and stramonium mixtures it has largely displaced. However, had artane not

1. Martin, J. P. Social Aspects of Prescribing. London, 1957.

proved its worth during the course of sporadic and haphazard employment over the course of a few years by thousands of doctors—at a time when it was still an expensive and untried drug—the benefit of this advance might never have been extended to the majority of patients with parkinsonism. This process of assessment could have been expedited by the early commission and publication of controlled therapeutic trials. Modest expenditure on this branch of clinical research would be an economic investment: for example, a small-scale investigation in this department [2] defined the limited role of one of the more expensive modern anticonvulsants in the management of epilepsy, and has probably rendered its widespread routine employment a little less likely.

The third type of expensive drug—the special preparation or combination of banal remedies—is an Aunt Sally for the critic, and indeed the marketing of expensive hæmatinic *olla podridas* and unholy combinations of vitamins and sedatives by otherwise reputable firms greatly strengthens the hands of those who would like to restrict the doctor's freedom to prescribe. But in fact many of the preparations in this group are extremely valuable. The long-acting effect of a spansule of phenobarbitone may make all the difference in the control of the difficult epileptic whose fits occur in the early morning. And although hard words have been used by purists about multi-vitamin preparations it would be negligent as well as doctrinaire to withhold them in the complex and ill understood metabolic disturbances manifested by a malnourished alcoholic or a patient with an obscure malabsorption syndrome.

It is clear also that the cost of drugs cannot be considered in isolation from other aspects of medical care. The prescription of oral penicillin in massive dosage in place of the less expensive injection not only may be imperative in the needle-shy child but also may be economic in a distant farm-labourer with a respiratory infection, to whom each visit may involve opening half a dozen moorland gates. Six months of tofranil for a depressed patient may push up the national drug bill by £30. The fact that such expenditure has saved £300 by averting admission to hospital will be sought in vain among Ministerial statistics.

That some doctors indulge in what some other doctors regard as over-prescribing cannot be doubted. But attention is less frequently drawn to *under-prescribing* by doctors who for one reason or another—sometimes undoubtedly for fear of administrative criticism from above—fail to give their patients the benefit of expensive remedies scientifically validated as outstandingly effective. In the same way it is often inferred that the higher average cost per prescription encountered in more prosperous localities [1] is due to extravagant or "excessive" prescribing. Since this high average prescription cost also correlates with a lower than average morbidity, a decreased frequency of prescription per patient, and a smaller than average number of patients per general practitioner, it could be quoted with at least equal justification as demonstrating a high and effective standard of medical practice worthy of more widespread emulation. Attractive though the economical doctor may be to the administrator, evidence is lacking of any correlation of low-cost prescribing with professional efficiency, and it seems improbable that even a Treasury officer would regard such parsimony as a quality to be sought in the choice of his own medical attendant.

2. Wilson, J., Walton, J. N., Newell, D. J. *Brit. med. J.* 1959, i, 1275.

In fact, although the view that extravagant prescribing makes a material contribution to the national drug bill is evident in much that is said and written on the subject, any factual basis for such a suspicion is lacking. It is certainly implicit in two measures which have been repeatedly recommended in the hope of holding back rising expenditure—limitation of the quantity of drugs to be permitted on a single prescription, and the employment of cheaper remedies where this is possible. The first of these is unexceptionable so long as it is not applied in the case of the very large number of chronic patients, in every branch of medicine, who require permanent or long-term maintenance dosage with relatively infrequent professional attendance. Any limitation of the quantity of drugs available on a single prescription in these cases would materially *increase* the cost of treatment, besides wasting the time of the doctor and the dispenser. Indeed the contribution of any restriction of quantity could hardly be more than to discourage such waste as now occurs in the treatment of acute illnesses.

The frequently reiterated Ministerial exhortation to employ cheaper remedies wherever possible presents greater difficulties, and is indeed not easy to reconcile with a deeply ingrained professional attitude of doing the best possible for each individual patient. It is easy for a Civil Servant to write such a recommendation into a memorandum but a very different matter for the doctor to offer something "second best" to a sick patient. We are indebted to a distinguished academic colleague for a practical suggestion towards the resolution of this ethical difficulty—that a small hospital be established for the carefully controlled assessment of cheaper treatments. He suggested that such a hospital might perhaps be situated conveniently for Whitehall, so that it could at once serve the physical needs and satisfy the public spirit of senior Civil Servants and politicians.

Conclusions

The desire to find a scapegoat to be held responsible for any unpalatable occurrence is universal, and is evident in the tendency to saddle the doctor, the patient, or the pharmaceutical industry with responsibility for the rising national drug bill. It is our contention that this is in fact the inevitable price of the present scientific revolution in medicine. The benefits of this revolution are evident in almost every field of vital statistics, as well as in an inscrutable but enormous reduction in the total amount of suffering in the community. But they cannot be obtained unless they are paid for. The tempo of medical research shows no signs of slackening, but rather the reverse. It is worth noting that the pharmaceutical industry alone spends a sum of money on research each year which is appreciably greater than the total annual budget of the Medical Research Council: even in the matter of basic pharmacological research its output dwarfs anything that can be achieved with the inadequate facilities afforded in the exiguous pharmacological departments of the universities. Unless the pace of research slackens—in which case neither the medical profession nor the industry will deserve well of the public—the drug bill, like the cost of the Health Service as a whole, is bound to rise. Whether such an increase need outstrip increasing national productivity is not a problem for the doctor. In the meanwhile an annual increase of 3·4%, at a time of previously unparalleled progress in therapeutics, seems to us to have caused quite disproportionate surprise and alarm.

PRIORITIES IN SOCIAL WELFARE

ADDRESSING the National Council of Social Service on Dec. 8, Prof. FRANÇOIS LAFITTE suggested that since 1948 we had been trying to extract a quart of welfare and defence from a pint of resources. As a result our actual social programme differed from the proposals of the famous blueprints for post-war social reconstruction.

The blueprints had presupposed a massive investment in re-equipping the social services with buildings and institutions good enough and diverse enough to serve the widened aims of social policy—health centres, small welfare hostels, secondary modern schools, hospitals, dental clinics. In fact 1954 was the first post-war year in which the physical volume of capital resources put into the social services (including education) even reached the inadequate level of 1938. Until we had got over the hump of rearmament and the housing boom, in real terms the claims of the health service were " frozen " and education was confined to its " essential fabric ". However, by 1958 the health service was allowed to take 10% more real resources than in 1951 (all the increase occurring since 1954); but top priority was given to education (which received an increase of 36%).

Turning to the future, Professor Lafitte foresaw that the margin of public funds for welfare in the nation's budget would rise from initially £70 million a year to at least £400 million a year by 1964. This could either be returned to consumers, through tax reliefs, for individual enjoyment, or used to improve the social services for communal enjoyment. A central issue of public policy was how to balance the claims of individual and communal enjoyment. A large part of the " welfare margin " was already earmarked by the Government for improving education. Eventually education was likely to need up to £200 million a year extra. Education remained the Government's no. 1 priority. " It is also mine," Professor Lafitte added, but he thought that after 1965 we could hope for a refurbishing of the health service's assets, to be followed in the early '70s by a housing boom, as the post-war " bulge " of children and their nearly as numerous successors took to marrying and home-making.

Since the war precedence had been given to the social services which help the ordinary family—maternity and baby welfare, family allowances, schooling, libraries, and medical and dental care. Without neglecting these common services ought we not, he asked, to be doing more for the minorities with uncommon needs? If society did not adequately provide for those who needed support to offset handicaps, could it really be proud of how well it cared for the social needs of the normal majority? We should face the fact that economic advance was steadily bringing the mass of wage-earners into the lower middle-class income ranges. It would be well for society if policy did more to quicken the spread of some of the lower middle-class virtues, such as budgeting over longer periods than a week or a month, and setting money aside for emergencies and old age. Most ordinary earners were being carried so far above a subsistence standard of living that it was becoming steadily less reasonable to want a social policy which assumed that no great number of fully employed citizens could house themselves decently unless the State built the dwellings and subsidised the rent; or that hardship was caused if people had to pay any appreciable part of the cost of welfare milk, school meals, spectacles, dentures, and other simple requirements.

In view of the growing prosperity of the ordinary citizen, Professor Lafitte would himself select, after education, the following social priorities:

Services for the mentally ill or handicapped should be humanised and transformed in the direction of community care and aftercare. Policy was already committed to this reorientation, but its implications had scarcely yet been studied. Its attraction was that it would avoid institutionalisation; its danger was that it might mean a transfer of defenceless souls from skilled to less skilled care—or to no care at all. If properly carried out, it would not be cheaper than the old method: it would be more humane and sensible.

Diversification and re-equipment of penal institutions were urgent, because they were nearly all presupposed by the Criminal Justice Act, which it was becoming fashionable to decry before it had been given half a chance to work effectively.

Family welfare services should be remodelled and perhaps fused to form a general all-purposes service.

Services for handicapped minorities were still inadequate and often less effective than they could be, because of their multiplicity.

Extra age benefit for the over-seventies would recognise advanced old age as a special handicap. Most old people of today had lived through two world wars, two post-war inflations, and an era of mass unemployment. Their chances of saving must have been minute, compared with those of the present working population.

Social work and training should be expanded, for the " underdog " services were also undermanned services.

Teenagers and the Bulge presented society with a challenge which we had partly failed to meet. The main improvements in education would come after they had left school. We kept adolescents at school longer than we used to, yet they matured earlier; and we had not really learnt how to handle, and what to teach, teenagers who were neither bookish nor intellectual, and who were no longer children. For the first time in history working lads and girls had the means to assert their independence by dressing, spending, and behaving in distinctive ways. If some of them went off the rails, were they not less to blame than the inflated economy, which gave them the means to snap their fingers at Dad, and the earlier neglect of their education?

MEDICAL JOURNALS FOR DOCTORS IN DEVELOPING COUNTRIES

THE British Supporting Group for the World Medical Association invites doctors in the United Kingdom to participate in a project for the regular supply of used British medical journals for doctors in " underdeveloped " countries—more especially in the Commonwealth—who, for various reasons, have at present little or no access to British medical literature. A pilot experiment for doctors in India is to be started early in the New Year. The scheme is to be essentially personal, an individual donor of used journals being placed in direct postal contact with an individual recipient. The honorary secretary of the British Supporting Group will provide a stamped and addressed envelope or wrapper to the donor, who, once a month, will post his journals to the recipient allotted to him. The journals which it is proposed to invite donors to send are the *British Medical Journal*, the *Practitioner*, and *The Lancet*.

The scheme will, it is hoped, help to disseminate knowledge of British medicine and its methods among doctors in less developed territories. The journals will be of value not only to individual readers or groups of readers, but

also in forming a nucleus for a local reference library.

Doctors who may be willing to take part are invited to get further information from the honorary secretary of the British Supporting Group for the World Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

BIRTH CONTROL IN AMERICAN POLITICS

FROM A CORRESPONDENT IN THE UNITED STATES

CONTRACEPTION has become a major political issue here. Last July the Draper Committee, who had been appointed by President Eisenhower to consider foreign military and economic aid, said in their report that the United States should give help, to nations that asked for it, " in the formulation of practical programs to meet the serious challenge " posed by populations growing beyond their means of support; and, answering a question, General Draper said that birth control was in the committee's purview. This recommendation, which has not been acted on, attracted little attention until, in November, the Roman Catholic bishops issued a statement opposing " any public assistance, at home or abroad, to promote artificial birth control."

This statement has been criticised by other religious groups. The head of the National Council of Churches (a Protestant organisation which, like the Roman Catholic Church in America, claims 39 million adherents) said that the decision of a President should be for his individual conscience and not be determined by the Roman Catholic Church—though he thought that private agencies would be a more suitable source of birth-control information than the Federal Government. The New York Board of Rabbis said that birth-control aid should be given to countries that requested it. But President Eisenhower (a Presbyterian) has said emphatically that birth control is not a proper Governmental responsibility. He expressed respect for the Catholic Church, for which, he said, " this thing has . . . religious meaning "; and though he added " this has nothing to do with Governmental contacts with other Governments ", it is widely held that his disclaimer is partly at least in deference to Roman Catholic views—especially since he made no adverse comment when the Draper Committee's report was first published, and it is said that it was on his insistence that the committee considered birth-control assistance.[1]

The Protestant Council of the City of New York (which recently led the successful fight to make birth-control instruction legal in the city's hospitals) has complained that the contrary views of members of Protestant communions should also be taken into account, and a Presbyterian writer said that if the President's deference to the beliefs of certain sects was carried to its logical conclusion he would not let the Government contribute to armaments, because the Quakers are pacifist.

The question has assumed political importance, not because of a split along party lines—many prominent Democrats have endorsed the President's attitude—but because at least two of the aspiring candidates for the Presidency next year are Roman Catholics, and the attitude of each to this issue may be taken as an indication of how his religious beliefs might affect his actions in general if he were elected President.

There is some irony in the debate about American aid to foreign countries to promote birth control when many American States have laws restricting birth control; for instance, a Connecticut State law prohibits the use of contraceptive devices and forbids doctors to advise their use, even to save the lives of patients. This law is being challenged before the Connecticut Supreme Court of Errors, and on Dec. 22 the court unanimously upheld the " constitutionality " of two 1879 statutes which forbid the presenting of or use of birth-control drugs or devices.[2] The plaintiffs, Dr. C. Lee Buxton, chairman of the obstetrics department at Yale University, and five unidentified patients of his, have announced that they plan an appeal to the Supreme Court.

1. *New York Times*, Dec. 6, 1959, sect. E, p. 3.

Personal Papers

AFTER NEARLY THIRTY YEARS

Plato says in *The Republic* that " the most skilful physicians are those who, from their youth upwards, have combined with the knowledge of their art the greatest experience of disease; they had better not be robust in health and should themselves have suffered from all kinds of illnesses." This method of instruction is not included in the medical curriculum and is fortunately imposed on only a few doctors. Being one of this group and having had a full dose of Plato's prescription in my mature years, I propose to submit his theory to the test of my own experience.

The illness was severe but never clouded my brain. On the evening of Feb. 17, 1930, after a few hours' premonitory symptoms, I became paralysed from the waist downwards, from transverse myelitis, while I was well on the way to recovery from a brief severe septicæmia. The paralysis, which I unexpectedly survived, left a considerable legacy of disability, principally affecting locomotion, bladder, and bowel—a spastic paraparesis. Certain aspects of this illness have already been recorded.[3–5]

THE PATIENT'S FIRST QUESTION

The illness was considered hopeless, absolutely so. I myself was well aware of its gravity. Nevertheless, the next day I asked my physician: " What do you think are the chances of my recovery? " He replied without hesitation: " I really do not know. If I were pressed for an answer, I should say fifty-fifty." I was in no mood to dispute this kindly verdict; so I thanked him and said it was very encouraging, and we left it at that.

On the twelfth day the distinguished brain surgeon, the late Sir Percy Sargent, kindly came to see me. Before he left he came to my bedside and said, very, very kindly: " I have now got a complete grasp of your case. It is very rare. I have seen only two similar cases. I cannot tell what is going to happen to you, but I can say this, that I do not see any absolute reason why you should not, ultimately, almost completely recover, except for a slight weakness of the peroneal muscles of your right leg." This verdict, to one still completely paralysed, was a wonderful exhibition of clinical skill. In my completely darkened sky, Sir Percy placed the bright star of hope. That star never set. He had, however, no expectation that I would survive. No-one could have been more astonished than he, when we met about a year later at the meeting of the Association of Surgeons in Belfast; he himself told me so.

These answers throw a little light on the vexed question of what the doctor should tell a patient suffering from

2. *ibid.* Dec. 23, 1959, p. 1.
3. Disabilities and How to Live with Them; p. 114. London, 1952. (Published by The Lancet Ltd., 7, Adam Street, W.C.2.)
4. *Lancet*, 1955, ii, 25.
5. *ibid.* 1956, ii, 35, 1256.

hopeless illness. He should not tell him anything disagreeable unless the patient really wants to know. He should not tell a lie. He should recognise the cases in which the truth is a relief from doubt, uncertainty, and fear. He should never forget that he may be wrong. He should speak very kindly and always if possible leave a ray of hope. The second answer was worth the world to me.

THE EMOTIONAL REACTIONS

It is the emotions that rule the lives of men. In sudden severe illness the emotions are deeply stirred. They should not be lightly interfered with. The emotional complex of different people differs as much as their faces do, built-up by the daily habits of years. A crisis, such as an illness, should not be used to upset them.

Very curiously I had no emotional reaction to the actual onset of paralysis. The tragedy had happened, and I simply accepted the fact. There was no pretence about this, and I was—and I felt—as cheerful as before.

The true meaning of this equanimity became apparent on the evening of the ninth day. I was alone. The fire had died down. It was a dull dismal evening in late February. Suddenly there swept across my mind a full realisation of what had happened to me; that I, laid in bed, could do nothing but raise my arms and move my head from side to side on the pillow; that I might continue to be utterly helpless as long as I lived, till death should release me. All at once I could have shrieked and shrieked in a frenzy of despair. What I did was to say to myself that this was not a nice thing to think about, and that I must think of something nice. In a few moments the spectre fled, and I was calm again. A horrid thought like this must be routed at its first onset.

It recurred—only for a moment—the next evening. And never again.

On the eleventh day, a peculiar choice faced me—the free choice of life or death. I said to my surgeon, on his morning visit, that I was on a slippery slope and if no change occurred would die in precisely four days. He agreed that this would happen unless I resumed taking nourishment, and suggested Bengers food. I was very emaciated. Fourteen days earlier, I had been put on a waterbed to prevent bed sores because I was so thin. For 11 days I had (by my own desire) lived on nothing but water and oranges (6–8 a day). I was mere skin and bone. It was a dreadful choice. Without telling her why, I put the question to my wife, the other person deeply interested, whether it was worth my continuing to live, even if paralysed. She replied emphatically: " Yes ". So I asked for Bengers food. After all, the other choice would have meant a cowardly exit from life.

These emotional reactions are of great interest. The delayed emotional upset, in its lateness, its suddenness, and its intensity is not unique, nor characteristic of a doctor. The absence of an hysterical outburst is due to the medical training. It is explained by Dr. John Brown in *Rab and His Friends*. The medical students at Edinburgh Infirmary were on their way to the theatre to watch an operation for advanced cancer of the breast. This was about 1815, before the days of anæsthesia, and it must have been a dreadful spectacle. " Up ran the youths, eager to secure good places; in they crowded full of interest and talk. ' What's the case? ' ' Which side is it? ' Don't think them heartless: they are neither better nor worse than you or I . . . in them pity—as an *emotion*, ending in itself or at best in tears and a long drawn breath, lessens, while pity as a *motive* is quickened and gains power and purpose." This diversion or redirection of the emotions from their ordinary passive manifestations into an active channel is an essential part of the training of a doctor. The ordinary manifestations of an emotion cause mental confusion and paralysis of action. Its diversion into channels of activity induces presence of mind and stimulates helpful action. This trained instinct prevented the hysterical attack.

On the twelfth day, I had a further diversion of the emotions. From the moment that Sir Percy Sargent implanted in me the hope of recovery, all my emotions and all my spiritual, mental, and physical powers were directed to one purpose—recovery. It was my single aim, my distant goal.

LEARNING TO WALK AGAIN

I learnt to walk as a child does, instinctively, by trial and error, by repeated effort. The beginning was slow and required patience. Not till six days after Sir Percy's visit did the first flicker of movement appear in my great toes. I have a vivid memory of my happiness, the next day, when I could move both great toes. Then in slow succession came movement of all the toes, the ankles, the knees, and in the end the hip-joints. My excellent Swedish masseur came for an hour a day, seven days a week, and on the day when I first got out of bed, precisely three months from the onset of paralysis, I was able to walk to and fro in front of the fireplace holding on to the mantelpiece: surely a triumph for massage.

Three weeks later I left the home for the seaside:

> " Like a child sent with a fluttering light
> To feel his way along a gusty night." *

just able with stick in my right hand and my nurse on my left to walk slowly and uncertainly a little way. Henceforth, the master word was perseverance, day in, day out, several times a day. It would be idle to describe the detail, since Nature adapts with great precision the technique suited to each case; but there is one point I should like to dwell upon.

I learnt very soon that I was doomed to fall frequently, and this has gone on all through the years. It was not a defect of balance, for I could stand on either leg; but if my balance was upset my legs were so slow in moving that they could not always save me. I found out in time all the causes of upset, but it was not always possible to avoid them. Later on, I set myself to learn the art of falling safely (and if possible, gracefully) by diligent practice in a big room. This was invaluable. I also learnt and practised the special technique for rising unaided. Let me give an example of the value of such practice.

I was coming out of the front door of a Scottish hotel (many years later). On the landing was a wire mat, which curled up as I stepped on it, and caught my foot, precipitating me head foremost down five steps on to the hard ground. I at once took three measures for protection. I used my stick on the steps, and broke my fall a little. I tilted my body to the left side, and dropping the stick extended my arms. I fell rather heavily on my left side, with no other injury than a bruise over my left great trochanter. Presently I got up, and went into the hotel to give a friendly warning to the proprietor. I then came out to resume my walk and found the mat already removed !

Constant practice, plus a very rapid reaction-time, enabled me to convert what might have been a nasty accident into a negligible mishap.

I had, perforce, to bestow some thought on the analysis of my defective walking. The general weakness of my legs

* Bird-Parliament, by Edward Fitzgerald.

very quickly improved, but I was never able to regain good power in flexing my hips and so had a shuffling gait, especially in my right leg which had a slight drop foot as Sir Percy had prophesied. But my main defect was spasm of the muscles of the lower part of my back, and the posterior muscles of the back of my leg, which slowed all the movements. I never could clearly understand why the voluntary impulse from my brain should be not just weakened, but distorted or diverted so that my legs refused to do what I told them.

SLEEP

As soon as movement returned to my legs, I began to be troubled with nocturnal jerks, keeping me from getting to sleep and awaking me from deep sleep. The simple and obvious remedy was sedative drugs. My night nurse and I discovered a much better way.

We found that the chief cause was too hot feet. It cannot have been easy to find this out, as I had lost the sensation of heat and cold as far up as the ankle. By cooling the feet and sometimes the legs, I got to sleep, only to be wakened in $^1/_2$–$1^1/_2$ hours by kicking legs. The nurse would then cool the feet or legs and turn me over and I would go to sleep at once. This would be repeated at least six times each night, and yet I would get a good allowance of refreshing sleep.

Sedatives or tranquillisers should not be used as symptomatic treatment until an intelligent effort has been made to discover and to remove the exciting cause. Such drugs are not good for morale. The jerks have continued for thirty years, and have never required treatment with drugs.

THE RETURN TO WORK

It was my full intention to return to my work as surgeon before the end of the year, but, as the hospital committee did not understand that this was possible, I was asked to go for review to London, as suggested by Sir Percy Sargent. The late Dr. George Riddoch, whose work on injuries of the spinal cord during the first world war made him the acknowledged expert on this subject, gave his verdict in the beginning of December: " You must return to work on Jan. 1. This is not a piece of advice, it is an order. You will, so far as your disability is concerned, soon be equal to your full work, and will be able to complete your full term as surgeon to the Royal Infirmary." This clear definite verdict, remarkable for its accuracy and its clinical acumen, was most valuable to me and enabled me to meet with full confidence all the difficulties that face the disabled man on his return to active life. For my part, although I had had considerable acquaintance during more than twenty-five years with the Workmen's Compensation Act of that day, it was not until I faced the problems of my own return to work that I fully realised the many hardships and often the unhappiness and anxiety that the disabled workman had to endure.

MY DOCTORS AND NURSES

Since the above verdict, I never had a doctor (save for two minor incidents) during the next twenty-five years. The explanation was simple. In 1930, the treatment of paralysis, especially the spinal type, was neglected. It would have been difficult at that time to find a doctor who would have believed in my recovery or could have helped me. This had one great compensating advantage. It left me free to live my own life, not under doctor's orders, to carry out my full duties as surgeon and as citizen, to drive my car, to golf, to walk the moors, to climb—in short to live the full joyous happy life, with the spice of adventure in addition.

My nurses were wonderful: they had worked with me, now they cared for me. In particular they saved me from bedsores, no small feat. They went about their work with the ease and grace which attend competence and experience. Associated with them was one, not herself a nurse, who devoted to me an unwearying care, a courage and initiative, and a sound practical common sense, without which my recovery would have been quite impossible—my wife. My sickroom was a happy place. A good nurse makes a good patient.

THE URÆMIC EPISODE

About the age of 73 my health began to fail. The symptoms of uræmia were atypical, and the urinary symptoms masked because of the automatic bladder. After about three years I became disinclined to walk, ceased to perspire, was thirsty, ate poorly, and lost weight. I was advised to have my blood-urea taken. It was 64 and was passed as high normal. About two months later, after a short tour to Scotland, it was 138. I disbelieved this, because I had never had any headache and could still drive my car 200 miles in a day. A fortnight later it was 158, and I was given an ultimatum. I was ill-suited for operation. My skin was in a poor state, an old scar had broken down and refused to heal; my bladder was chronically infected; at operation the bladder which for years had been contracted, with very thick wall and a maximum content of 6 oz., was found to contain 40 oz. of retained urine. Under local anæsthesia, with all precautions, a suprapubic cystostomy was performed. My blood-urea a week later was 120. The operation has achieved the maximum of success. At the present time, more than two years later, I am well and independent. My bladder drains through the permanent suprapubic opening, by means of a self-retaining Foley catheter, which I change myself every six weeks. The wound and the tube channel are healed. There is no leakage and no discharge and I wear no dressing or belt. For years I have worn an appliance for the prevention of double inguinal hernia, and to this my bag by day and my tube by night are fixed. I have no urinary symptoms whatever. For this excellent result of an operation which has not a good reputation, I owe a great debt to my surgeon. There was no emotional reaction, nor any occasion therefor. A good surgeon makes a good patient.

THE SETBACK

This was the great surprise of my life. I was convinced that my spinal lesion was quiescent after twenty-nine years. The way in which it flared up is perhaps worth describing in detail.

On Monday, July 27, 1959, returning home after a frugal lunch, I felt sleepy and sat down on an easy chair, my legs supported from knee to foot on another chair. When I awoke, I could not move my left leg. After waiting a few minutes, I managed to struggle to my feet, and, with the aid of my stick and the furniture, to reach the hall. There my left foot trailed and I fell. I pulled myself up by means of a chair, and in about ten minutes the left leg returned to normal. I walked quite normally round the lawn to the summerhouse: as I stood beside it my left leg suddenly lost all its power and I nearly fell. I then, after a minute, was able to walk normally into the house, when suddenly it failed again for a minute. Thereafter, for three complete days I was in my usual health—motoring, walking, and going round a hospital. On retiring to bed after three days I found that both legs had lost power to a serious degree. The next morning I could just dress and attend to myself, and walk with short shuffling footsteps and trailing left leg, aided by my stick, across the lawn. The old spasticity in my back had returned.

I slowly improved but after three weeks my legs were completely fatigued after 100 yards. After three to four months I had steadily returned nearly to my old state of health. My whole technique as regards movement had to be delicately readjusted. I can again walk slowly as far as $^1/_2$–1 mile in a day, drive the car with ease and freedom, but am more spastic than I was. I have still no idea of the cause of this setback.

SUMMING-UP

This simple tale shows the unity of the human organism, body, spirit, and mind. This illness, a paralysis, might have been regarded as purely physical. The record shows that it excited powerful emotional reactions. The emotions were diverted from their normal outlet into channels of purposive activity. They stimulated the intelligence, so that the spirit and the mind, acting together, dominated the body, and raised it to the highest level that the remaining disabilities would permit. At this level, body, mind, and spirit acted in as perfect unision as in the healthy human being.

There are few who would go so far as Plato and wish their doctor to have many illnesses; but this tale supports Plato's thesis that a doctor who has an illness learns the better to understand his patient's feelings and acquires a deeper understanding of his art.

X.Y.Z.

The Widdicombe File

LVIII.—HEARTBREAK HOSPITAL

DEAR JACK,

It was good of you to send us a Christmas card, early as always; and a very merry Christmas to you, too, and to your staff, God bless them! It was in their position in that very hospital (as you probably well know) that I spent my first Christmas as a junior resident, for my sins; and whatever sins I may have had—and they were many—I reckon I just about got up to date with them there. That, of course, was before they made you the Surgeon, so doubtless times have changed. It was a shattering experience which haunts me still, and I'm thankful that my physical stamina (carefully nurtured by six years' studious neglect of work) got me through. Let me tell you about it: I need to get it out of my system.

It's really not so long ago that I found myself at that loosest of loose ends where you've got no prospect of employment the next month but the mortgage has to be paid. Thus it was that my desperate postal pleas reached your St. Beezum's Hospital—lately the Wapchester Municipal Institution, or, as it was familiarly called, the Golden Gates of Wapchester. Faltering steps led me to a great grey gaunt building, rising, all slate and dirty brick and crowned by the regulation water-tower, from a sea of monotonous black slum roofs. It was enfortressed from the surroundings (? to keep the patients in) by a huge wall and gates of immense size. In response to my tinklings a gloomy porter creaked them open and led me solemnly over courtyards of decaying asphalt and sterile flowerbeds and by great blocks of seemingly deserted wards—somewhat after the manner of the boatman conveying the souls of the dead across the river Styx. He left me at last, alone in the residents' mess to take in a further dismal scene. The room was decorated in old dark-green paint and crammed with heavy Victorian furniture: a decrepit sideboard contained some battered cutlery, mats, cruet, an empty jar of piccalilli, and yesterday's *Mirror*. A vast bookcase housed a few tattered *Lancets*, the Calcutta Review of Public Health for 1947, the front and back covers of *The History of the War in Pictures*, and *Anna Karenina* missing pp. 638–921. There was also an empty beer-bottle and, for some inexplicable reason, volumes of the *London Companion* for 1862 to 1875, bound neatly in leather. A torn and tea-stained cloth covered the table, and there were neither pictures nor fire. The clock had stopped at 7.23, and the room seemed to be lit by a 10-watt bulb. It seemed impossible that anyone could actually be *living* there—even the flies were dead. I turned on an elderly radio—some relic apparently of early electronic history, but the only thing I got was a strong smell of burning. A crone hobbled out of the nether regions: "'Ere, can't use that, it's busted." She examined me more closely: "You the new doctor? Didn't tell me you was coming they didn't, ain't got yer room ready". With which hearty greeting she disappeared into the ground.

This is just the introduction, setting the scene for you; but perhaps you would be bored by all the dreadful detail—the great cold bedroom on the third floor against which a diminutive gas fire battled valiantly but in vain—the awful plumbing noises and the trains that kept me awake on the rare occasions when patients didn't—the complete lack of recreational amenities apart from the nursing staff (not that we had time)—the food, oh the food, words fail me, ghastly hashed-up reheated slosh, armour-plated fried eggs, pastry like cardboard—the endless bickering with the hospital secretary which never got us anything but promises—and the hours! Half-day a week and one weekend in three gave me about a 140-hour week, and, with salaries then £350 less £100 for the appalling living quarters that I had no desire whatever to inhabit, I was being paid at about 8½*d.* an hour. I suppose it was terribly good clinical experience that I shall always be grateful for and all that, but it didn't strike me that way at the time. I should really have quit, I suppose; but one is very green and insecure round about the time of qualifying, and generally frightened of everybody. My maturer colleagues in the mess might have made a fuss, but being largely foreign they were uncertain of themselves too. It was, as you know, a busy hospital, and with two wards of 54 beds, mostly acute, I had enough to do. The prospect of reading up one's cases or studying for an exam was a quite laughable one.

You don't need to tell me that since then the place has been redecorated—they started before I left. But those old buildings need a lot more than the odd coat of paint. The coke boilers of circa 1875 won't usually stand the extra basins and radiators that make such a difference when the cold north-easter blows over the Pennines at this time of year. I know, too, that teaching hospitals often offer an even rawer deal to their young chaps, secure in the knowledge that the supply of eager applicants is unquenchable. It has been said, also, that your junior staff are now more numerous and that a television set will probably make their Christmas vigil a happier one; but I wonder! Is it true that you had no applications for your last H.S. vacancy apart from an M.D. (Skorblensk) of 58, reinstated by the G.M.C. last year after a number of drug offences? If this is true (and somehow I hope it is) it might make that dreary old com-

mittee of yours see the red light and do something at last. Married quarters would solve your problem, even if it did mean more building. A really solid staff shortage is the only thing, in my experience, to shift a lay committee—which is probably why so many dull old hospitals have such pleasant new nurses' homes.

Let's face it Jack, junior staff have a pretty bad time of it. Not so bad as in our day perhaps; but the increase in salary has scarcely kept up with the cost of living, and the hours, even now, are often atrocious. They don't usually know their rights (have your administrators shown the juniors the Ministry circular on Standards of Accommodation H.M.58/68—have they? I bet!), and when they do they are too insecure and scared to make a fuss. And not without reason, for it may be professional death to become known as a " trouble-maker ". I wonder if your medical committee has a junior staff representative yet? This proposal has been approved by quite exalted bodies—although often the behaviour of consultants at this function is far too disturbed to exhibit before junior gaze. However, a junior's presence is to be encouraged, if only to make his seniors act like gentlemen. One of our splendid representative bodies, not a hundred miles from Tavistock Square, is at present trying to compose a sort of *Guide Michelin* to hospitals in the N.H.S., and good luck to it. The trouble seems to be that the questionary is not getting through to the very chaps that should be filling it in: our region held a meeting not long ago and none of the junior staff there had heard of it. It's a modest affair concerned with matters of solid fact—none of the 5-star business yet—but I hope the next edition will be more enterprising. Good luck to it anyway; it is contributing, if meagrely, to the Millennium.

So a Happy Christmas to you Jack—and to your staff. Spare a thought for them as you carve the turkey in the bosom of your family on Christmas day, on Christmas day, on Christmas day in the morning.

Your old and affectionate friend,

RICHARD COBBLEIGH.

Public Health

The Registrar-General's Commentary

IN his commentary on the statistics for England and Wales for 1957 [1] the Registrar General remarks that the home population has been increasing by an average of 300,000 a year, in round numbers, since 1951, and in the twelve months mid-1956 to mid-1957 it increased by 240,000 to an estimated 44,907,000.

The " natural increase " (the excess of births over deaths) was 226,000 in 1956–57—a year of high birth-rate and low mortality. About 106 boys are born for every 100 girls, but the death-rates for males are higher than those for females at all ages; so at ages 0–4 there were 1053 males per 1000 females, at ages 30–34 the numbers were about equal, at ages 60–64 there were 770 males per 1000 females, and at ages 75 and over there were nearly twice as many women as men.

Births.—The 723,381 live births in 1957 were the largest number since 1949, and the birth-rate of 16·1 per 1000 population was the highest since 1950. This increase continued the upward trend which began in the late spring of 1955. (The 1958 rate was higher still, at 16·4.)

Marriages.—There were 346,903 marriages in 1957—6000 fewer than in 1956. The decrease was due to the smaller number of unmarried persons of marriageable age in the population. The marriage-rate—15·4 persons marrying per 1000 total population—was slightly lower than in 1956. The tendency to younger marriage is reflected in the proportion of grooms and brides who are under 21. For men it rose from 3·4% in 1938 to 8·7% in 1956 and to 9·6% in 1957; for women from 16·4% in 1938 to 32·2% and 33·6% in 1956 and 1957.

Deaths.—There were 514,870 deaths registered in 1957, the death-rate for both sexes being slightly lower than in 1956.

Infant mortality and stillbirths.—The infant-mortality rate was 23·1 per 1000 live births in 1957, and was the lowest recorded in England and Wales (the 1958 rate was lower still, at 22·5). More than 60% of the deaths occurred in the first week of life, but the rate for these deaths in the first week (14·1) was also the lowest recorded in this country. The stillbirth-rate of 22·5 per 1000 total live and still births was slightly lower than in 1956. Immaturity continued to be the chief cause of infant mortality.

Tuberculosis.—There were 4784 deaths from tuberculosis in 1957—11% less than in 1956. Deaths from respiratory tuberculosis fell by 12%, but for the first time for many years there was a small rise in the number of deaths from the non-respiratory form—from 522 in 1956 to 535 in 1957. There were no deaths from respiratory tuberculosis of boys aged 5–9 or of girls aged 10–14. Notification-rates continued to decrease, being 82 per 100,000 population for males and 49 for females. Mass miniature radiography units made 3,514,600 examinations in 1957; the number of cases found by these units was 22% of all cases of respiratory tuberculosis notified. The highest incidence of cases was again found among persons referred to the units by general practitioners.

Cancer.—Deaths assigned to cancer in 1957 numbered 94,017 (50,056 male and 43,961 female), the highest numbers yet recorded. The largest increase in cancer mortality in both sexes since 1936–39 has been from cancer of the lung. Cancer of the lung accounted for the highest proportion (nearly a third) of all male deaths from cancer in 1957 and for about 6% of all female deaths from cancer.

Diseases of the circulatory system.—In 1957 there were 188,630 deaths assigned to diseases of the circulatory system and a further 73,669 to vascular lesions of the central nervous system, which together accounted for 51% of all deaths.

Accidental and violent deaths.—There was a decrease in 1957 in the number of deaths due to accidents and violence, which numbered 21,561 compared with 21,870 in 1956.

1. The Registrar General's Statistical Review for England and Wales, 1957, Part III, Commentary. H.M. Stationery Office. 1959. Pp. 299. 16s. 6d.

Registration of Food Premises

In his annual report for 1958, Dr. J. H. Briscoe-Smith, medical officer of health for St. Marylebone, describes a sharp outbreak of food-poisoning, involving two schools, in which 62 pupils and staff were affected. The cases were spread over seventeen local-authority areas; and, apart from verbal notification of the original case, only 3 cases were notified. Had this outbreak resulted from consumption of food in a restaurant it might have remained undetected or, at best, investigation might have linked the 4 notified cases.

". . . the control of detected cases of food-poisoning and their contacts, though essential, is much less likely to be effective than a direct attack on the source of the infection by the close supervision of every place where food is produced, prepared, handled or eaten to ensure that every precaution is taken against its contamination. . . . The registration of all food premises is long overdue and it is a sad commentary on the present state of the law that while one shopkeeper selling packaged ice-cream from a refrigerator is required to register with the local authority, his next door neighbour selling frozen foods is not required to do so. Many of these foods such as made up meat and fish dishes, some of which may be prepared as far afield as Italy, are, if not stored properly, potentially at least as dangerous as ice-cream and are much more liable to contamination during manufacture."

In England Now

A Running Commentary by Peripatetic Correspondents

IT is an unhappy Christmas Day tradition in most hospitals for the senior surgeon to carve the ward turkey, usually with a display of ill-concealed inaptitude both anorexigenic and alarming to any patient about to undergo surgery. It is also customary to cast the pædiatrician in the role of Father Christmas at the children's party and this, too, is an unsatisfactory arrangement.

To begin with, the disguise is hot and uncomfortable. One frequently trips over bits of trailing robe, and wisps of cotton wool have a propensity for invading oto-oro-rhinological orifices with irritating consequences which may render inadequate control over blasphemous interjection. For a few children the appearance of Father Christmas is the signal for a prolonged and piercing howl, unappeased by a chorus of a dozen shameless brats to the effect that " He's not Father Christmas at all, but that nasty doctor who gave us the needle the other day!"

Having restored some semblance of order (a semblance being all that is ever feasible on these occasions), one must then begin the dangerous business of distributing the presents. The opening of the first parcel is the cue for a mad onrush of hordes of small children and, notwithstanding a bodyguard of stalwart nurses, the little horrors are liable to swamp trees, parcels, presents, Father Christmas, and everything. It is an unfortunate trend of our times to provide children with all manner of warring implements, and Father Christmas at once becomes the ready target for a variety of missiles ejected from crossbows, pop-guns, catapults, water-pistols, and so on. Some of the little devils are so preoccupied with fighting that they fail to answer when their names are called. Then, every now and again, some juvenile impostor will claim a parcel destined for someone else, who soon raises a vociferous condemnation of this outrage. To mete out justice under these circumstances merely serves to transfer noise from one source to another. A final difficulty, for which there is no remedy, is that some child has to have his present last of all. A prolonged wait does nothing to enhance appreciation. Either he has one like it already only better, or it is the wrong colour, shape, or size, or perhaps neighbouring destructive influences are brought to bear at an early stage.

Thank heaven I have seen the last of Christmas for the next twelve months.

* * *

I have already spent a fortnight in bed with influenza, but I am glad to stay in for a few more days, for the weather is terrible. A gale with slush and snow is blowing and everything is in disorder, because every year the winter comes as a great surprise to this country. The papers are full of descriptions of 300 cars in one big mass on the main road to Copenhagen. All the trains are stuck at Glostrup because the signals are frozen. The ferry from Elsinore to Hälsingborg cannot carry the international sleeping-cars, because they are too heavy and the ferry will tip over in the wind. And a woman in Busserup had her child before the midwife arrived, late in the snow.

All this makes soothing reading when you are in bed and have time to read Professor Blackett's article in the *New Statesman*. I think it's time Britain and Denmark and other countries stopped making or buying atom bombs and concentrated on getting a bit of gravel on the roads to help the midwife to get to Busserup in time.

* * *

Thirty years ago, my straw hat and a noisy packet of crisps held in a sweating hand, with boils on my neck, I was impelled on and down, down into the pit (*9d.*) by sex, a dirty word in those days, by posters declaiming " The Eternal Eve ". I huddled into the plush seat thankfully. No prefect had spotted me. Through the miasma of the years I still recall the pervasive smell of patchouli, those gorgeous stark Dietrich legs, the insolent heavy-lidded vulpine stare, and the soul-freezing stuff that only U.F.A. Studios could produce—" Kiss me, my fool ". My heart bled for poor dear old Emil Jannings, haggard and humiliated, even for his fatuous *furor teutonicus* and the universal and grimy Weltschmerz.

Last week my children took me to *The Blue Angel* and we sat in pseudo zebra-skin tip-ups, through a pervasive smell of Heavenly Mist. But the saucy tone-deaf child-siren with flaring nostrils and android hips had little to offer, even with her race-horse legs thrown in. My sour heart did not thrombose over the agitated and vulgar domestic peccadilloes. The film was all too evilly refined and morbidly tiresome. Yet as the lights went up a lad with boils on his neck and a straw hat in his hand hurried out. I thought he looked like any other boy; but my children said he looked rather like me.

* * *

Routine laboratory work may appear dull and humdrum, but it has its rewarding moments.

The young, newly promoted student technician in blood-transfusion had laboriously completed his first routine examination of samples of blood from the antenatal clinic. The ABO groups agreed, the Rh groups, using two different anti-D sera, agreed, and the antibody tests were also in agreement. The long afternoon session was at an end most satisfactorily. I turned to him and said, " That's wonderful." He sighed and, with heightened colour and sparkling eye, he replied, " It's not wonderful, it's a ruddy miracle."

* * *

Americans are an oral nation and no mistake. As part of the universal milk-and-honey, there is an immense proliferation of candy, milk-bars, chewing-gum, and cigars. What with Hollywood, teenagers, and baby-dolls, kissing has become the major industry and a prime raw material for export. But alas! cigarettes are already under sentence, cranberries are suspect, and now another subtle blight has fallen on the unhappy land. Long-suffering rats, painted year by patient year with lipstick dyes, have at last developed tumours. Suddenly the American skies, the biggest and bluest ever, are darkened. Lipstick is out, goodbye glamour. Whatever will be the effect of it all? The women's strike fomented by that arch-shop-steward Lysistrata averted war, certainly; but probably only because the men were too busy arguing with their wives to fight the enemy. What will happen now that oral aggression can no longer take its rightful avenue? Shall we see a bitter outburst of frustrated verbal savagery and a renewal of international discord, or will there merely be a boom in American milk-sales?

* * *

CHRISTMAS NIGHT IN THE DOGHOUSE

Nowell, nowell, nowell, nowell!
That may be what *you* say—I say what the hell:
You say, Christmas comes but once a year—
What do you expect me to do about it? Cheer?
And if you do, for precisely that reason
I hereby resolve to scrub round all compliments of the season
Of robins giblets and fetch your own blooming log
As well as of all pushing characters with something to flog.
As the commercial buildup gets huger and huger
Personally this person gets Scrooger and Scrooger.
So resisting all those spiels
With hark the herald thank you Sirs and sticky seals
Let them, I say, decorate their tents prefabs and baronial halls
With luminous glass bodgers and little balls—
At the sight of a cracker tears
Run down my nose for all you victims of racketeers
And when I think about the lolly
Spivs make annually out of the craving for holly
Anyone who in my hearing mentions Bob Crachitt
Is going to catch it.

Hark the Herald Angels sing
  Gramophones and plastic string:
Rheum and reindeer, crackling, carols,
  Slipping discs, and rolling barrels.
Gourmandising grub and culture,
  Christmas hastens our sepulture—
May you at this festive season
  Get the chance to name your poison.

Letters to the Editor

USE OF THE TERM "SUPERFEMALE"

SIR,—I hope that nothing I say will be regarded as any reflection on the importance of Jacobs et al.'s [1] demonstration of the existence of an XXX chromosome pattern in a woman with hypoplastic genitalia, but I must own to a certain satisfaction on seeing Dr. Stern [2] cast doubt on the propriety of the name "superfemale". Though their letter of Dec. 19 answers part of Dr. Stern's objections on genetic grounds, I think from a more general point of view it is possible to criticise "superfemale". This name has the important advantages of being memorable and being inapplicable to any other syndrome, but it is frankly misleading as a clinical description. Moreover, it has an emotional element which should be avoided, if possible, in the terms we use in speaking of patients with this kind of disorder. Dr. Stern's alternative of "metafemale" avoids the positive error but falls into the opposite one of vagueness: there is a large class of cases to which the term metafemale could be applied (all the varieties of female pseudohermaphroditism, for instance) and only arbitrary definition can confine it to the sense he proposes.

Surely there is a far simpler solution in the use of the chromosome constitution as part of the name? The chromosome constitution is the best definition of the syndrome, and it could simply be called the "XXX syndrome". One could similarly resolve arguments as to the names of other syndromes with chromosomal anomalies. If one introduces the XXY into the name of what I used to call chromatin-positive Klinefelter's syndrome, there can be no ambiguity as to what one is talking about. The "XXY syndrome" would suffice, though most people will probably prefer to use "XXY Klinefelter's syndrome" or some such phrase. The Turner's syndrome complex is more difficult, simply because it is a complex, but if the results of Harnden and Stewart [3] prove to be generally applicable, it may well turn out to be justifiable to speak of "XO Turner's syndrome" for the classical cases and "XY gonadal dysgenesis" for the cases without stigmata. Mongolism might well be called "22-trisomy" if we are to carry this out logically—though here, of course, we are handicapped by the absence of an agreed nomenclature for any of the chromosomes except the sex chromosomes.

As Ben Jonson so wisely said, "A man coynes not a new word without some perill, and lesse fruit; for if it happen to be received, the praise is but moderate; if refus'd, the scorne is assur'd. Yet wee must adventure". It *may* be premature to use chromosome constitution in definition and naming. But the advantages would be great, and the risk I think slight. "Wee must adventure"!

Department of Pathology,
Western Infirmary,
Glasgow. BERNARD LENNOX.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—I have read many papers like that of Dr. Simpson (Dec. 12) advocating that cavernous hæmangiomata should be given "expectant treatment", that pompous locution for doing nothing. None of them brings out two important points. The first is that many dreadful disfigurements, particularly of the face, begin as tiny red spots, either present at birth or appearing in the first month. Nobody knows what would happen if they were efficiently treated at this stage, since they are quite invariably dismissed as trivialities; it would be interesting to find out.

In spite of preaching for years that a growing red spot on a baby's face is a surgical emergency, I have never yet had one referred to me at this stage by a general practitioner; but I have picked up a few and treated them. The results suggest that the process of regression can be started very early in the growing stage by producing inflammation in the abnormal tissues.

The second point is what happens to the cases which disappear from these inquiries. It is undeniable that many mothers, in horror at what is happening to their babies' faces, seek the aid of surgery. It would be interesting to know how many.

London, W.1. DENIS BROWNE.

SIR,—I read with interest Dr. Simpson's article of Dec. 12. It only goes to prove how misleading statistics can be, and what large numbers must be studied.

All are agreed that cavernous angiomas disappear in the course of time, but they are likely to leave atrophic depigmented areas; not infrequently they undergo spontaneous ulceration which results in a cure, but the resulting scar is apt to be disfiguring.

I should like to quote from a paper by Andrews et al.[1]

"The records of 1113 patients with angioma who were observed at the Columbia University-Presbyterian Medical Center between 1932 and 1955 were studied. Of these, 329 had hemangioma simplex and 584 had hemangioma cavernosum. Of the 153 patients with hemangioma simplex who received no treatment, 102 could be observed adequately. The lesions of 64 (63%) involuted or improved within 5 years, whereas those of the other 38 (37%) persisted after 5 years. Of the hemangiomas simplex which involuted spontaneously, 83% were 1 cm. or less in diameter. It may be concluded that any hemangioma simplex on the face measuring 1 cm. or more should be treated promptly, since it is unlikely to undergo involution without therapy. The danger of ulceration of hemangiomas on the lips, nostrils, eyelids and ears suggests that these should be treated even though less than 1 cm. in diameter.

"Of the cavernous hemangiomas of 135 patients who received no treatment during the first 5 years of life and who could be followed adequately, 22 (16%) involuted or improved within 5 years. The lesions of 113 (84%) persisted more than 5 years. This high percentage indicates the desirability of treatment for all cavernous hemangiomas."

I think there is a great tendency to exaggerate the frequency with which congenital hæmangiomata undergo spontaneous involution and disappearance.

I should also like to refer to a paper that Dr. E. Millington, radiotherapist at the Royal Sussex County Hospital, and I read at the Brighton and Sussex Medico-Chirurgical Society in 1953.

In a survey made at the various hospitals in Sussex and Kent of 1752 cases of angiomas, 814 received X-ray therapy, the criterion of recovery being the maternal satisfaction in all cases. The treatment consisted of one, two, or three treatments of 400–600r repeated at 6-monthly intervals. 200 cases in the series required treatment after the 5-year period, and only 20% cleared in the first year. In a personal communication, Professor Trueman-Nelson confirmed the view borne out by these results.

The series by J. Walter, of Sheffield, comparing 83 untreated cases with 88 treated was too small. By choosing an equal number of patients at various periods in our group these figures could be confirmed and contradicted.

The late Dr. Roxburgh believed that although a large

1. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., MacGregor, T. N., Maclean, H., Harnden, D. G. *Lancet*, 1959, ii, 423.
2. Stern, C. *ibid.* p. 1088.
3. Harnden, D. G., Stewart, J. S. S. *Brit. med. J.* 1959, ii, 1285.

1. Andrews, G. C., Domonkos, A. N., Torres-Rodriguez, V. M., Bembenista, J. K. *J. Amer. med. Ass.* 1957, **165**, 1114.

number of cavernous nævi show a marked increase in size in the first 6 months of life, they usually disappeared spontaneously, but there is another less common type, quite indistinguishable, which tends to increase in size, but does not disappear at the 5th year, and indeed often increases in size at this age.

If cavernous hæmangiomata are alleged to clear spontaneously how is it that so many are met in adult life?

Hove, Sussex. E. COLIN-JONES.

INTRATHECAL PHENOL AND RELIEF OF SPASTICITY

SIR,—I wonder if I might be permitted to make a few comments on the papers by Dr. Nathan and by Dr. Kelly and Dr. Gautier-Smith in your issue of Dec. 19.

Dr. Nathan and Dr. Kelly will, I am sure, recall that Dr. Maher and I have long been interested in this particular manœuvre, for they contributed in a very agreeable and informed way to the discussion on a paper which I gave on this subject in April, 1959. Perhaps I might add that Dr. Maher and I at this very moment have a paper on our experiences with this technique in the hands of the Editor of another journal.

The earliest occasion in which we used this technique was in the case of a patient with a hemiplegia who was treated by Dr. Maher in April, 1956, and it is quite satisfying to report that this patient is still ambulant in December, 1959. Another patient with multiple sclerosis and painful flexor spasms which made sleep impossible for her was first treated in November, 1957, and again in January, 1959, because of recurrence of the spasms. This accords with the experience of Dr. Nathan and Dr. Kelly, who had both found that reinjection proved very helpful.

We are all well aware of the disadvantages of the method. I was interested to note that Dr. Nathan mentions the danger of paralysing the sphincters. Our experience has been that the most probable affection of bladder function is that of retention; cystometrograms in such cases have demonstrated that the bladder muscle is atonic but the sphincter is not paralysed. A short period of tidal irrigation has resulted in recovery of bladder function within the space of three to four weeks in most cases of this nature, but in one of them it was necessary to resort to bladder-neck resection (Mr. T. Moore).

Dr. Kelly finds that phenol in myodil is more satisfactory, but our experience has been that its effect is of relatively short duration, and the use of this particular combination seems to interfere to some extent with the later effect of phenol in glycerin. One has the impression that the deposition of the myodil solution round the nerve-roots in some way prevents subsequent use of phenol in glycerin from producing its full effect. We have used the glycerin solution in ambulant patients, but our practice is to try 2% rather than 5% solution in such cases, in order to avoid diminution of motor power.

Although Dr. Nathan has found little change in the constitution of the C.S.F. following the introduction of phenol into the theca, we have found that the protein in certain cases may rise as high as 400 mg. per 100 ml., but, as he says, the meningeal response is surprisingly mild.

One point of philosophical interest emerges. One gathers that Dr. Nathan and Dr. Kelly were carrying out their clinical experiments simultaneously with our work, although they do not mention any precise dates of the cases which they describe in detail. It seems that this is yet another example of the creative urge of the Zeitgeist.

Department of Neurology,
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Manchester. L. A. LIVERSEDGE.

SIR,—The two articles on intrathecal phenol follow closely the experience in this unit, where the original Maher technique has been used and spasms have been relieved satisfactorily.

Dr. Nathan pools his solution at the anterior root. Dr. Kelly and Dr. Gautier-Smith have their patient in the lateral position, which would presumably affect both roots, but more the posterior one. In a short series of mine the posterior roots have mainly been affected. These differing methods have all produced relief of spasms, though it would appear that Dr. Nathan's method gives a more permanent result, and this must be due to his concentrating on the anterior root. In the future I think this will prove to be the method of choice in most cases, but it may well be that in those patients where an attempt should be made to conserve residual voluntary movement, a relatively "weak" phenol solution concentrated mainly on the posterior root would be best. If this failed a strong solution could always be used later, on the anterior root.

The following two cases are of interest. The first because of a considerable recovery of voluntary power, the second because it involved the treatment of a spastic arm.

(1) A woman with cervical spondylosis and bilateral severe flexion and adduction spasticity of the legs with flexor spasms. A number of intrathecal blocks relieved the spasms and unmasked enough voluntary movement and power in one leg to allow her to push herself up the bed when she slid down.

(2) A young man with spasticity of arm and leg after a head injury (no spasms). His fingers were digging into the palm of his hand and producing pressure sores. 3 ml. phenol (1:15 in glycerin) at the cervical level relieved the spasticity and uncovered voluntary movement of the hand. He then had a weak but very useful grip.

Finally, two questions. One to Dr. Nathan, who mentioned the danger of paralysing the bladder sphincters: has he had any complications of this nature in his series and if so to what degree? The other to Dr. Kelly and Dr. Gautier-Smith: it would be valuable to know their criteria for deciding what concentration of phenol to use (the range 5–20% is rather large).

I found the two articles of great interest and much value.

Regional Neurosurgical Centre,
Liverpool. S. LIPTON.

THE CONVALESCENT EXCRETER OF SALMONELLÆ

SIR,—In a recent annotation [1] on the treatment of salmonella carriers, you discussed the possible value of furazolidone ('Furoxone'). At that time only one clinical paper [2] dealing with this drug had been published. Since then more articles have appeared.[3–6] These reports are concerned with the treatment of a total of 271 patients, of which 255 became symptom-free after three to five days' therapy with furazolidone. 105 were shown to be suffering from infections with one or more strains of the following organisms: shigella, salmonella, escherichia, staphylococcus, streptococcus, giardia, entamœba, and proteus.

4 patients who were suffering from *Shigella sonnei* infections were not cured by chloramphenicol. After subsequent treatment with furazolidone a clinical and bacteriological cure was obtained. In addition, the patients with the protozoal

1. *Lancet*, 1959, ii, 501.
2. Ponce de Leon, E. *Antibiot. Med.* 1957, **4**, 814.
3. Baddeley, H., Baird, T., Fletcher, F. *Med. Pr.* 1959, **242**, 172.
4. Turnbull, T. A. *Med. Proc. S. Afr.* 1959, **5**, 423.
5. Nassa, A. *Brit. med. J.* 1959, ii, 1063.
6. Rettig, J. H. Scientific Exhibit, American Medical Association Meeting, Atlantic City, 1959.

infections (11 in number) also became symptom-free and showed negative stool-cultures after therapy. In all of these investigations no side-effects other than very occasional nausea and vomiting were experienced.

Your annotation also referred to the treatment of *Salmonella typhimurium* infections in fowls with furazolidone, and it was stated that most of the birds which survived became chronic "carriers". In human gastrointestinal infections, however, this has not been shown to occur; few patients continued to carry this, or other pathogens, after treatment.

The presence of pathogenic organisms in the stools was demonstrated in 105 patients. After treatment, 97 showed negative stool-cultures, but the remaining 8 continued to harbour pathogens.

The only work on the treatment of carrier states is by Hobson,[7] who investigated the action of furazolidone in mice made "carriers" of *S. typhimurium*. Treatment with high doses of this drug freed 8 out of 16 mice from this organism. In another group of 16 such carriers that received no treatment, only 1 mouse freed itself spontaneously from the pathogen.

Smith Kline & French Laboratories,
Welwyn Garden City, Herts. I. SCHRIRE.

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—In reply to Dr. Køster (Dec. 26) may I say that (1) Operation is indicated if the patient has renewed massive bleeding after admission to the hospital or if such a condition continues after admission. Massive bleeding is a condition where it is impossible to keep the blood-pressure normal without continued transfusion.

(2) The age of the 6 patients who died unoperated upon was between 70 and 92. 3 patients had such a severe cardiac insufficiency that operative treatment was presumed contra-indicated for they could not even be transfused. 2 patients died in the first two hours after admission despite transfusion. Because of his age, the patient of 92 years was not operated on although he did have renewed bleeding.

Drammen, Norway. OLAF RØMCKE.

SIR,—I should like to support Mr. Lytton's remarks (Dec. 26) concerning patients with melæna, but without hæmatemesis, and in whom no diagnosis is made.

An identical case to Mr. Lytton's was treated in this hospital in 1957, and another stomach was lost needlessly, the bleeding coming from a small hæmangioma about 0·5 cm. in diameter, involving the anti-mesenteric border of the jejunum about 4 feet from the duodenojejunal flexure.

This man, aged 45, was admitted in November, 1957, with a severe attack of melæna of 3 days' duration, with no associated dyspepsia. Transfusion was undertaken, but further heavy melæna produced unconsciousness which recovered with subsequent rapid transfusion.

At laparotomy on Dec. 15 no abnormality was found, but the jejunum and ileum were full of blood. A blind partial gastrectomy was undertaken, but the bleeding continued and it was decided to undertake a further laparotomy on Dec. 20. On this occasion there was blood only in the ileum, and a small jejunal lesion was indicated by a leash of vessels running towards the acute mesenteric border, but no underlying thickening or ulcer could be felt. Resection was undertaken and the lesion proved to be a necrotic jejunal hæmangioma.

His subsequent progress was uneventful, apart from the development of an incisional hernia, and when he was last seen several months ago his general condition was excellent.

In this case there had been a careful search of the small intestines, but the lesion was missed on the first occasion. On the second occasion it was relatively easy to find the lesion as the jejunum was empty of blood.

Hackney Hospital,
London, E.9. R. F. READ.

7. Hobson, D. *Brit. J. exp. Path.* 1956, **37**, 20.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—In your leading article of Dec. 19 you wonder whether early enthusiasm has made too light of the disadvantages of these drugs, using insulin as a standard of reference. This may be so, but I feel it equally pertinent to wonder whether we are too complacent in our attitude to insulin. Insulin is not satisfactory replacement therapy in diabetes, such as thyroid is in myxœdema or as cortisone is in Addison's disease. It could more closely be compared to the use of folic acid in pernicious anæmia. Insulin has saved and prolonged the life of thousands of diabetics but at the same time it permits the development of the most devastating complications, even in so-called mild diabetics. I have observed that some diabetics whom we have designated as "failed tablets", because while taking tablets their blood-sugars remained above normal, showed equally poor control when transferred to insulin. But we were more prepared to accept hyperglycæmia in these patients on insulin, because even if the treatment were unsatisfactory, at any rate it had nearly 40 years of orthodoxy behind it. Whether hypoglycæmic agents will be more or less effective than insulin in preventing long-term complications in "mild" cases remains to be seen.

There are two aspects of oral hypoglycæmic agents not treated in your leader that I feel are worthy of mention.

First, in many new diabetics who initially fail to respond to diet alone but who are controlled by tablets, remission of the diabetic state occurs after normoglycæmia has been maintained for about six weeks or so. If the tablets are discontinued after this length of time, in many diabetics good control continues on the same or a greater diet than was originally ineffective. In my opinion, newly diagnosed diabetics should not continue to take tablets indefinitely without establishing at some point that a remission has not taken place.

Second, since the sulphonylureas and the diguanides have a different mode of action, some diabetics who cannot achieve normoglycæmia on either preparation alone may do so on a combination. A combination of chlorpropamide and phenformin is the most effective oral hypoglycæmic therapy available today.

Finally, you state that the risks of toxicity seem to be less common with chlorpropamide than with tolbutamide. I feel wider experience with chlorpropamide is necessary before this can be substantiated. Sensitivity drug rashes are commoner with chlorpropamide, and whereas the therapeutic dose of tolbutamide can be exceeded with impunity, increasing the daily dose of chlorpropamide above 500 mg. daily can give rise to jaundice and vertigo, suggesting a narrower margin of safety than with tolbutamide.

London, W.1. ARNOLD BLOOM.

DENTISTS AND ANCILLARIES

SIR,—Your annotation of Dec. 5 may lead some readers to suppose that there is a shortage of candidates for training as dentists. This is not so. Candidates commonly apply to three or four schools in the hope of obtaining a place at one of them. The serious situation is that the number of places available annually in the United Kingdom is only about 620 although the need is for at least 900.

We anxiously await the fulfilment of the Government's intention to increase the number to 890 and trust that replacement of the cramped and obsolete buildings of dental teaching hospitals will no longer be delayed.

Department of Dental Medicine,
Guy's Hospital, London, S.E.1. MARTIN A. RUSHTON.

PENICILLIN IN LEPTOSPIROSIS

SIR,—In your columns Dr. Semple [1] criticised previous letters [2 3] which suggested that penicillin is of value in the treatment of leptospirosis. He referred to his own article [4] in these terms: " The fact remains that a properly controlled trial has been done. The only way in which this can be refuted is to show some fundamental defect in the trial, or to produce contrary evidence from another equally or better controlled series."

The report of this trial contains only one detailed set of figures for scrutiny. These are in the form of a scatter diagram showing the day of illness on which the treatment was started, and the day on which patients became free of signs and symptoms (which are not further defined). Analysis of this diagram (see table) shows that the control group and the group treated

ANALYSIS OF CLINICAL TRIAL OF PENICILLIN IN LEPTOSPIROSIS

Group	Number	Treatment	Day treatment started		Day free of signs and symptoms	
			Mean	Standard deviation	Mean	Standard deviation
A	31	Control	4·0	1·7	7·8	2·7
B	21	Penicillin	4·7	1·2	6·0	1·8
			$P > 0.10$		$P < 0.02$	

with penicillin did not differ significantly in the time at which treatment or observations commenced, but that the duration of signs and symptoms was significantly shorter in the penicillin group.

The figures calculated from this diagram do not agree with those given in table III by Dr. Fairburn and Dr. Semple, presumably derived from the same data. There the duration of signs and symptoms for the control group is given as 10·8 days, and for the penicillin group as 9·7 days. Does the ordinate in the diagram perhaps refer to duration of signs and symptoms after treatment? If so it does not say so, and in any case the figures should then be 11·8 and 10·7 days respectively. This difference approaches, but does not reach, significance at the 5% level. " Duration of signs and symptoms " seems a very subjective criterion on which to base an assessment, and one would like very much to study similar scatter diagrams showing total duration of fever and duration of fever after treatment.

The distribution of serotypes in their control and treated groups is quite different. Indeed, in more than half of the control series the infecting serotype remained unidentified. The clinical severity of the diseases produced by different serotypes varies greatly. It seems reasonable therefore to demand that studies of the efficiency of treatment should concern a single serotype, or that the groups compared should have a similar distribution of serotypes. This is a difficult criterion to satisfy, as identification of the infecting serotype is never available until at least some weeks after the patient's admission. It is, however, of interest that Dr. Semple applied this criticism to the series of Mackay-Dick and Robinson,[5] but not to his own paper.

It is contended, therefore, that the results reported by Dr. Fairburn and Dr. Semple do not justify their sweeping conclusions that " penicillin and chloramphenicol play no useful part in the treatment of uncomplicated leptospirosis in British troops in Malaya, and we suggest that these antibiotics are unlikely to be of value in the treatment of leptospirosis elsewhere ", because (i) their groups are not comparable in serotype distribution and (ii) even so, their figures can be used to support the value of penicillin if one ignores some inconsistencies in them.

Clinical experience in North Queensland, supported by analysis of 264 cases,[6] is in complete agreement with the opinions of Mackay-Dick and Cook that penicillin is of value. The practitioners in the area, when approached in 1953, considered that it was not justifiable to withhold treatment from patients. It was not, and will not be, possible therefore to attempt a controlled clinical trial. The same situation may well apply in other areas where leptospirosis is a common disease. It would be most desirable that the detailed figures of the clinical trial reported by Dr. Fairburn and Dr. Semple should be submitted to tests of statistical significance.

Queensland Institute of Medical Research, Brisbane, Australia. R. L. DOHERTY.

***Dr. Doherty's letter was shown to Dr. Semple and Dr. Fairburn and their reply follows.—ED. L.

SIR,—We should like to comment on the points raised by Dr. Doherty and also to quote some of the statistical results in our controlled trial on the treatment of leptospirosis.[4]

(*a*) The relevant symptoms and signs were recorded carefully every day on a standard chart by the same two observers. The point at which they had ceased is a good guide to the length of the illness and marks the time when the patient is beginning to get up and about. These are not merely " subjective criteria " therefore.

(*b*) Any confusion over the ordinate of the scatter diagram can be clarified by consulting the text of our article [1] under the Results section: the ordinate being " the day on which the patient became free of symptoms and signs after the start of treatment . . ." If the mean results from this diagram are added to the day treatment started (table II), then the total duration of symptoms and signs will be overestimated by one day, because there is a day of illness common to both figures. We consider this is the reason for Dr. Doherty's thinking the figures in table III to be incorrectly quoted.

(*c*) Dr. Doherty has shown that the time to become free of symptoms and signs from the start of treatment is significantly shorter in the penicillin group. Because this does not take account of the day of the illness on which treatment was started it is not possible to assess reliably whether penicillin has shortened the total duration of the illness. The first treatment day in each individual patient cannot be ignored on the grounds that there is no statistical difference between the mean day of the illness when treatment was started in the control and penicillin groups. Indeed analysis of our results [4] (table III) showed that there was no significant difference between the control and penicillin groups as regards total duration of symptoms, signs and the total time to become free of both symptoms and signs ($P > 0.1$ in all cases).

(*d*) We found a similar pattern as regards the length of pyrexia. We first compared the duration of fever in hospital of the penicillin and control groups—this relies solely on the day-to-day taking of the temperature and on no " subjective criteria ". The mean difference between the two groups was only 1·5 days (penicillin the shorter), and this was not statistically significant ($P > 0.1$). By adding the days of illness before admission, and presumably then getting an estimate of the total length of fever, there is still no significant difference between the two groups ($P > 0.05$). There is, however, a significantly shorter period of fever after treatment, but this again does not take into account the time at which treatment was started in the illness, as in section (*c*) above.

To sum up, our statistical results showed that penicillin did not significantly *alter the natural course of the disease* when compared with the controls and those treated with chloramphenicol. Also, as pointed out in our trial [4] (table IV), even when treatment with penicillin was started early (before or on the 4th day of the illness) the average length of the illness was not shortened; in fact, the average

1. Semple, S. J. G. *Lancet*, 1959, ii, 289.
2. Mackay-Dick, J., Robinson, J. F. *ibid.* 1959, i, 100.
3. Cook, A. T. *ibid.*, 1959, ii, 81.
4. Fairburn, A. C., Semple, S. J. G. *ibid.* 1956, i, 13.
5. Mackay-Dick, J., Robinson, J. F. *J.R. Army med. Cps*, 1957, **103**, 186.
6. Doherty, R. L. *Austr. Ann. Med.* 1955, **4**, 53; *ibid.* 1956, **5**, 23.

number of days taken to become symptom-free and sign-free was greater when treatment was started early. We do not, therefore, see any inconsistencies in our results and believe that it would be wrong to use Dr. Doherty's analysis of our scatter diagram to support the use of penicillin in leptospirosis.

(*e*) Now, as to leptospiral serotypes: it is not possible to arrange an equal distribution between control and treated groups. Dr. Doherty feels that in a study of the efficacy of treatment there should be a similar distribution of serotypes, as he believes the clinical severity varies with the infecting serotype. Trimble [7] in an analysis of 236 cases in Malaya showed that there was absolutely no correlation between clinical severity and serotype. Analysis of our own results [1] also showed that the severity of the illness and the incidence of complications bore no relationship to any serotype or serogroup. This, combined with the knowledge that as far as we know, all serotypes are sensitive to penicillin,[8] makes it unnecessary, even though desirable, to ensure an equal distribution between treated and control groups. It does not support Dr. Doherty's contention that the results of our clinical trial should be rejected because of this unequal distribution. We agree, however, that it invalidates one particular criticism previously made concerning the use of controls from another time period.[9] Nevertheless we still feel that in a clinical trial of treatment in leptospirosis it is desirable that controls and treated patients should be selected in a random manner and compared at approximately the same time period by the same observers—even when, as in this instance, it results in an unequal distribution of serotypes.

We do not think that there is anything "sweeping" or inaccurate in our statement [4] that "penicillin and chloramphenicol play no useful part in the treatment of uncomplicated leptospirosis in British troops in Malaya . . ." Our reasons are as follows: (1) Penicillin (or any other antibiotic) has never been shown to affect the mortality of the disease nor the incidence of the complications, jaundice, oliguria, or anuria.[4 10 11] (2) In our controlled trial [4] there was no significant effect of penicillin on total duration of pyrexia, symptoms, and signs as compared with the controls. The mean results show that the length of illness was slightly shorter in the penicillin group. The well-recognised variability of leptospirosis, common sense, and our statistical analysis suggest this a chance finding. If it was real and due to penicillin it was marginal and of doubtful value, especially when balanced against the discomfort of frequent intramuscular injections over several days and the other disadvantages of massive antibiotic therapy. Above all, it is in complete disagreement with the reported dramatic effects of penicillin elsewhere [12] and makes nonsense of any suggestion that controlled trials are unjustifiable in this instance.

The Maudsley Hospital, London, S.E.5. A. C. FAIRBURN.
St. Thomas's Hospital Medical School, London, S.E.1. S. J. G. SEMPLE.

THE ABNORMAL APPENDIX

SIR,—In his article of Dec. 26 Mr. Jewers referred to my work on this subject. His thoughtful paper confirms the two conclusions at which I arrived in 1952, namely:

(1) There is no such thing as the "conservative treatment" of appendicitis. If one ever considers conservative treatment it is in relation to peritonitis and never to appendicitis, which is a different thing. The treatment of appendicitis, when the necessary facilities are available, is to remove the appendix. The only condition under which conservative treatment is logical is where the inflammation has spread beyond the appendix and peritonitis is present, the decision then for operation against conservative treatment being a nice one to be made with every ounce of the surgeon's lifetime's experience.

(2) Appendix abscess is now the most dangerous of all the situations resultant on appendicular inflammation.

London, W.1. W. SKYRME REES.

EVENING COLIC IN INFANTS

SIR,—Professor Illingworth's views on the management of screaming infants are of considerable importance to family doctors. In his report (Dec. 19) on the trial of dicyclomine hydrochloride in evening colic in infants he shows that, of the 15 babies who received active drug and inert substance, each for a week, 9 had higher scores with the drug, 3 had equal improvement with drug and control, and 3 improved more with the inert substance than with the drug. There were also four scores of +3 and two of +2 with the inert substance.

Do these figures really justify his conclusion that the drug is of considerable value?

St. Mary Cray, Kent. E. TUCKMAN.

VASODILATOR DRUGS IN OCCLUSIVE VASCULAR DISEASE OF THE LEGS

SIR,—The conclusions arrived at by Mr. Gillespie [1] cannot be allowed to go unchallenged.

Mr. Gillespie measured the blood-flow in the foot and calf of patients with and without obliterative arterial disease after intravenous injections of four so-called vasodilator drugs. He concluded that, as the vasodilators he used did not increase the calf-muscle blood-flow and often decreased it, all prescribing of vasodilators for the treatment of intermittent claudication is useless. The vasodilator drugs he used were tolazoline ('Priscol'), phenoxybenzamine ('Dibenyline'), chlorpromazine ('Largactil'), and promazine.

I have found that tolazoline is the least active peripheral dilator used in my series, and I have abandoned the use of phenoxybenzamine in the treatment of obliterative arterial disease. Chlorpromazine and promazine are not claimed by the makers to have any benefit in the treatment of this disease. By contrast, I have repeatedly shown [2] that spasmocyclone ('Cyclospasmol'), nicotinyl alcohol tartrate ('Ronicol'), and azapetine ('Ilidar'), used alone or in combination, are the drugs of choice in the treatment of peripheral vascular disease. It is ridiculous to condemn the action of satisfactory drugs on the basis of tests carried out with ineffective ones. In practice vasodilators are used either by mouth or by intra-arterial injection, and not intravenously. If Mr. Gillespie wished to disprove the action of vasodilators in the treatment of peripheral vascular disease, he should have used them in this way.

The symptoms of occlusive arterial disease develop rapidly after the disease has been present for some years. A minor decrease in the blood-flow must finally precipitate the first symptoms. The effective vasodilators increase the blood-flow sufficiently to ameliorate these symptoms. The method used by Mr. Gillespie to measure the blood-flow is not sufficiently accurate to detect small increases in the blood-flow.

The long-term effect of drugs in the body cannot be assessed accurately by any method other than clinical trial. The vast number of publications describing the advantageous clinical action of the various vasodilators is evidence of their value in the treatment of peripheral arterial disease.

Dudley Road Hospital, Birmingham, 18. R. O. GILLHESPY.

7. Trimble, A. P. *Proc. R. Soc. Med.* 1957, **50**, 125.
8. Schlipköter, H. W., Beckers, M. *Z. ImmunForsch.* 1951, **108**, 301.
9. Semple, S. J. G. *Lancet*, 1959, ii, 289.
10. Broom, J. C. *Brit. med. J.* 1951, ii, 689.
11. Ross-Russell, R. W. R. *Lancet*, 1958, ii, 1143.
12. Mackay-Dick, J., Robinson, J. F. *J. R. Army med. Cps*, 1957, **103**, 186.

1. Gillespie, J. A. *Lancet*, 1959, ii, 995.
2. Gillhespy, R. O. *Angiology*, 1956, **7**, 27; *Brit. med. J.* 1957, i, 207; *ibid.* 1957, ii, 1543; *Brit. J. clin. Pract.* 1959, **13**, 608; *Lancet*, 1959, i, 1096.

HERPETIC WHITLOW

SIR,—We read with great interest the article in your issue of Nov. 21 by Dr. Stern and his colleagues on herpetic whitlow amongst the nursing staff in a neurosurgical unit. We encountered somewhat similar cases of herpes simplex in the nursing staff a few years ago at a London hospital,[1] but, in addition to cases of whitlow and paronychia as described in this article, there were a few cases of an impetiginous type of infection. At first the lesions were like a bullous impetigo, although rarely we noted a small herpetic vesicle in the early stages. After that the lesions were more granulomatous like orf and ran a more indolent course than the pyogenic counterpart. We also found a distinct difference between primary and recurrent or, more probably, reinfections.

Primary infections, confirmed by virological and serological tests, invariably developed multiple lesions, but, unlike the cases described by Dr. Stern and his colleagues, we found a constitutional disturbance, fever, and regional adenitis to be common. In one of us who developed a primary infection as a result of collecting material for diagnosis from a case of herpetic gingivostomatitis a series of small vesicles appeared four days later around a minute skin abrasion, and after a period of about a week developed into a multilocular vesicle which subsequently took on the appearance of a granuloma. Pyrexia (100–101°) lasted for several days and regional adenitis was marked. In two cases of recurrent or reinfection in members of the staff with herpes-neutralising antibody at the time of onset, lesions were strictly localised to a single vesicle on the thumb or digit with a small area of surrounding erythema. It was also noted that this type of lesion healed very much more rapidly than the primary.

In all instances a clear history of contact existed, there being cases in the ward of generalised herpes simplex or eczema herpeticum. A senior nurse who developed a solitary lesion on the finger was also subject to recurrent labial herpes, but in this instance it appeared that it was not an autogenous infection but she had become reinfected from one of the cases of eczema herpeticum. In this latter disease the virulence of herpes virus seems to be enhanced by the patient's eczematous diathesis, and the infection is often alarming, sometimes fatal, and compared with other forms of herpes in a non-eczematous patient the risk of contagion is greater.

We also found the examination of smears taken from the base of the vesicles to be of value in diagnosis. The typical appearance of multinucleate epithelial cells, which are seen only in herpes simplex or varicella-zoster infections, enabled a diagnosis to be made within a few minutes, which could then be confirmed by further laboratory investigations.

R. T. BRAIN
J. A. DUDGEON.
London.

HYPOPARATHYROIDISM WITH STEATORRHŒA

SIR,—In view of the occasional interest shown in the combination of hypoparathyroidism with steatorrhœa (e.g., by Williams and Wood [2]), particularly since we drew attention to it in *The Lancet*,[3] it is only right that I should report the conclusion to the story of our first patient.[4]

Shortly after our report [3] appeared she returned to hospital with masses in the abdomen, which were found at laparatomy to be lymphomatous. This malignant growth had virtually replaced the whole pancreas and infiltrated the wall of the small bowel throughout its entire length. She died shortly afterwards outside hospital and no necropsy was performed.

1. Brain, R. T. *Brit. med. J.* 1956, i, 1061.
2. Williams, E., Wood, C. *Arch. Dis. Child.* 1959, **34**, 302.
3. *Lancet*, 1957, i, 1079, 1086.
4. Jackson, W. P. U., Hoffenberg, R., Linder, G. C., Irwin, L. *J. clin. Endocrin.* 1956, **16**, 1043.

The fact that the diagnosis of her malady was not idiopathic steatorrhœa, as we had suspected, makes no difference to the interest in its connection with hypoparathyroidism—the combination apparently including the symptom, "steatorrhœa", rather than any particular basic disease.

Medical School,
Groote Schuur Hospital,
Observatory, South Africa. W. P. U. JACKSON.

CRANBERRIES AND THANKSGIVING

SIR,—In the issue of *The Lancet* of Nov. 28, 1959, in the column devoted to Public Health (appearing two days after our American Thanksgiving had been observed in a literal welter of cranberry sauce), a comment on both cranberries and Thanksgiving is to be found.

In regard to the warning issued by the Secretary of Health, Education and Welfare pertaining to contaminated cranberries, it is pertinent to observe that Mr. Flemming, in calling attention to the situation, was doing only what the law requires, and Americans, as is well known, are a law-abiding people. The fact that a person would need to eat 15,000 lb. of contaminated cranberries daily for a long period to suffer any ill effect is a poor argument; many persons on this side of the Atlantic would gladly do so in order to defend a principle.

In the very first paragraph, in reference to the background of Thanksgiving, the suggestion is made that many of the Pilgrims failed to survive their first American winter and that those who did survive accomplished this feat because of a bountiful harvest. The sad fact is that the Pilgrims set foot on Plymouth Rock on Dec. 21, 1620, too late to harvest a crop that had not been planted, and that those who survived did so because of a mild winter, the friendliness of the still unconditioned Indians, and the British guts that they brought with them.

JOSEPH GARLAND
Boston, Mass. Editor, *The New England Journal of Medicine.*

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—Mr. Azie [1] has done well to direct attention to a method of resuscitating patients who are gravely ill from massive intraperitoneal hæmorrhage, and for whom blood-donor or blood-bank facilities are not available. This is the simple but strangely neglected procedure of injecting the patient's own blood back into the veins after straining off all obvious blood-clot. Autotransfusion, as it has been called, is particularly useful in the graver cases of ruptured tubal pregnancy.

The method is, however, by no means new. Dr. Logan,[2] working in a South African mission hospital, has recorded 40 cases of autotransfusion with recovery in every case. Dr. Markowski, working in Belize, British Honduras, has given me details of 100 cases of ectopic pregnancies so treated with survival in all but 1 case. So useful has he found this method that he has sterile apparatus, including a mechanical sucker, constantly available in his operating-room. The subject is discussed in Munro Kerr's *Operative Obstetrics* (6th ed., p. 761).

During the past 25 years I have used autotransfusion on many occasions. It is easy and can be used without the time-consuming matching and cross-matching of bloods. Working in a teaching hospital, I feel it a duty to demonstrate the method from time to time in order to impress upon students that this is a possible way of saving a patient's life when blood-banks and blood-donors are not available.

Mr. Azie does not appear to use any anticoagulant when collecting the blood. Were he to do so he would find that the

1. Azie, A. A. *Lancet*, 1959, ii, 1093.
2. *S. Afr. med. J.* 1948, **22**, 793.

method is even easier and more reliable. My practice has been to cup the blood out of the abdominal cavity by means of a small gallipot, to strain it through several layers of gauze in a glass funnel, and to collect the fluid portion in a sterile flask containing 2 g. disodium citrate and 3 g. dextrose in 120 ml. water (the normal " bleeding " flask kept for blood-donors). As soon as the first bottle is ready it is connected to the intravenous-saline drip apparatus which has been set up before starting the operation.

Naturally, only recently shed blood is suitable; but it is in the most urgent case of all—the ruptured ectopic pregnancy with massive intraperitoneal bleeding—that such blood is abundantly available. The method is less applicable, but is also less necessary, when intra-abdominal bleeding has already been present for several days.

It is strange that this simple procedure, which can be lifesaving in so many instances, is not better known. Perhaps the present-day availability of donor blood has made our younger surgeons contemptuous of the older and simpler methods of transfusion.

The Nuffield Department of Obstetrics and Gynæcology, The Radcliffe Infirmary, Oxford.

J. CHASSAR MOIR.

PRECORDIAL CATCH

SIR,—Allow me to add to the letters on the precordial catch—letters which may illustrate Dr. Asher's thesis that naming a condition brings it into clinical existence. I have no evidence to submit, but I should just like to record the naïve assumption that this pain is caused by some " catch " (a transient wrinkling, friction, or folding) of the pleural membranes.

Amsterdam.

P. J. THUNG.

URINARY INFECTION IN THE NEWBORN

SIR,—I was very interested in the paper by Dr. James (Dec. 5). I have been about to start a similar study and among other things had hoped to see if there was any correlation between cell-counts on uncentrifuged urine and the approximate cell-count per high-power microscopic field on centrifuged urinary deposit as used in most laboratories. Did Dr. James make any observations on these lines?

There has been an unusually high incidence of urinary infections in newborn infants in recent months hereabouts, fortunately none fatal. In one infant considerable jaundice and anæmia occurred, which appeared to be hæmolytic in origin, and as we were unable to find evidence of blood-group incompatability or other cause for the hæmolysis, we attributed this to the renal infection; the hæmoglobin and bilirubin on admission on the 10th day of life were 11·3 g. and 10 mg. per 100 ml., the latter rising to 15 mg. on the 11th day, and the former falling to 6·3 g. on the 29th day. Another infant had moderate jaundice and anæmia, again presumed due to the renal infection. It would be interesting to know if any of Dr. James' cases showed hæmolytic anæmia.

With regard to the mode of invasion of the urinary tract, it was suggested by Delaney [1] that in addition to the hæmatogenous route, infection may spread along the lymphatics to the kidneys, or ureters, from an infected umbilicus. The first infant mentioned above had a severe omphalitis, and the organism cultured both from umbilicus and urine was of the coliform group. It is remarkable that the three infants reported by Delaney with omphalitis and pyelonephritis each developed kernicterus, apparently unassociated with blood-group incompatability.

Few will disagree with Dr. James that treatment of urinary infections should be continued for not less than six weeks, with regular follow-up for a year or longer. I presume from her use of a fairly large dosage of sulphonamide for the first two weeks that Dr. James believes the main lesion in most cases of urinary infection to be pyelonephritis, an adequate serum level of the drug being required to combat the interstitial renal infection: such is certainly my view.

BRIAN MCNICHOLL.

1. Delaney, W. E. *J. Pediat.* 1959, **54**, 36.

INFLUENZAL ENCEPHALITIS

SIR,—In his letter of Dec. 19 Dr. McGill may be ascribing to corticosteroid therapy (" modern antiallergic therapy ") what is in fact the natural course of the disease. In the 2 cases I reported during the epidemic [1] the most striking clinical features were the severity of the illness and the unexpected rapid recovery. We did not use cortisone but only antibiotic cover. Our first case was in extremis for 3 days and the prognosis seemed quite hopeless. A very similar course was shown by case 2 of Dunbar et al.[2]

Of the 4 cases reported by McConkey and Daws [3] only 1 was treated with cortisone; and, although they noted " some clinical improvement " 4 hours after commencing therapy, she apparently remained in coma for a further 5 days and then " recovered consciousness rapidly ". It is hard to believe that the cortisone played a major role in the course of her disease.

Queen Mary's Hospital for Children, Carshalton, Surrey.

V. DUBOWITZ.

INSULIN REACTION AND DIABETIC RETINOPATHY

SIR,—It is accepted that well-controlled diabetic patients have less vascular complications than those under poor control. Patients are sometimes observed, however, whose vascular complications become progressively worse in spite of the ideal control of their illness with diet restriction and insulin. On the other hand, patients are seen who have had free diet and no insulin with no vascular complications.

We observed a 60-year-old man whose diabetic retinopathy appeared after insulin reactions,[4] and another whose retinal hæmorrhage occurred during a urine-sugar-free period on insulin treatment. The experiment of Dünner et al.,[5] which demonstrated that insulin produced retinal hæmorrhage in dogs, supports the possibility of the occurrence of such undesirable changes in the retina as observed by us. Fortunately, I found the recent article of Jahnke [6] about the unpleasant effect of insulin on the retina. He quoted several cases from the literature in which insulin seemed to provoke retinal changes. He pointed out that diabetic retinopathy has been increasing with the spread of insulin treatment, and that this increase is not merely due to the prolongation of survival of diabetic patients by the progress in treatment.

We speculate that the unfavourable effect of insulin may be due to an increased release of adrenocortical hormone, resulting from a fall in blood-sugar. Administration of cortical hormone or corticotrophin sometimes provokes microaneurysms and other changes in the retina. The recent studies of Saito et al.[7] again confirmed an increase in urinary corticosteroid excretion in diabetics with vascular complications, compared with those without complications. Basing his views on the experiments of Müller and Petersen,[8] Jahnke proposed increased permeability

1. Dubowitz, V. *Lancet*, 1958, i, 140.
2. Dunbar, J. M., Jamieson, W. M., Langlands, J. H. M., Smith, G. H. *Brit. med. J.* 1958, i, 913.
3. McConkey, B., Daws, R. A. *Lancet*, 1958, ii, 15.
4. Goto, Y., Fujino, K. *Endocrinol. japonica*, 1959, **6**, 9.
5. Dünner, L., Ostertag, B., Thannhauser, S. *Klin. Wschr.* 1933, p. 1054.
6. Jahnke, W. *Hippokrates*, 1959, **30**, 279.
7. Saito, T., Yagi, T., Sasaki, H., Otsuka, H., Hoshi, A., Uemura, J. *Tohoku J. exp. Med.* 1959, **70**, 247.
8. Müller, E. F., Petersen, W. F. *Klin. Wschr.* 1926, p. 1025.

of the blood-vessel wall. I feel that the strictly controlled state, where hypoglycæmia may occur, is harmful to diabetic patients, especially to those with retinopathy.

Philadelphia. YOSHIO GOTO.

OBESITY

SIR,—Professor Yudkin's article of Dec. 19 throws much light on the confused subject of obesity. Further clarification of the use of the term "overweight" and of the effect of excessive food intake seems desirable.

Overweight is determined by comparison of weight with accepted standards for age, height, and sex. It is a statistical concept, objectively determined by physical measurement and it is not constantly correlated with obesity. Obesity is basically an æsthetic, or at least clinical, concept, subjectively determined and produced by the distortion of body contour by fat.

I found in a series of 200 adult male patients seen consecutively in general practice that 3 muscular men were 40% over standard weight for age and height: they were certainly not obese. Similarly those with poor muscular development can be little overweight, or even of standard weight, and yet be obese. Clinical judgment, not comparison of weight alone, establishes the presence of obesity.

Common experience challenges the statement that "it is simply not true that most people—or any single person—can eat more food or less food without changing weight". Dodds,[1] in a discussion on obesity at the Royal Society of Medicine, referred to an experiment in which subjects whose weight had been constant for many years were kept in bed and given two or three times their normal diet. They did not increase in weight although controls put on weight easily. Such an observation seems very credible and it would be interesting to know whether it has been confirmed. There is nothing inherently improbable in the idea that certain people—even most people—are able to respond to excessive food intake by increased metabolism. I have not found in Professor Yudkin's article the evidence that this is not so.

London, W.2. JOHN MCMULLAN.

DIMINISHED RESPONSIBILITY

SIR,—Dr. Maddison (Aug. 15) advocates the doctrine of determinism. The "argument in brief", on its behalf, is that "the path which we take is unswervingly determined by our personality structure". In other words, we are determined, because we are determined. This "argument" contrasts unfavourably with the three proofs for free will.

Firstly, intellective consciousness apprehends immediately and experimentally, in the concrete, not only the act of will, but also its freedom. While we are deliberating or taking counsel, and while we are terminating our deliberations or consultations, we are quite conscious that the selected end is imposed on us by our own will, and that we are not irresistibly or necessarily drawn to it. Our intellective consciousness clearly distinguishes the action to which we are determined, from our free acts. When someone says "tree", I am necessitated to exercise an act of apprehension of "tree", and I have no consciousness of freedom. But when I go for a walk, or draw a line, I am conscious of acting from free choice, and that I can freely stop at any point. This immediate experimental evidence cannot be met by simply denying freedom. Nor can it be explained as mere ignorance of cosmic forces and laws.

Secondly, there are facts which cannot be explained unless freedom of choice be admitted. These include the making of plans, promises, and appointments; legislation; self-approbation, self-reproach, and remorse; the giving of commands and prohibitions, advice, rewards and punishment, praise and blame. We can act against our physical inclinations, as when we refuse a chocolate lest we overeat, or when we get out of bed early on a cold morning to go to Church. Surely the latter is not accounted for by a church-organist among my human ancestors, nor by a bat-in-a-belfry among my pre-human ancestors (if any).

The third and greatest proof of freedom, from the objective infinity of the human intellect, is too long for exposition here.

Because there are things in man which are chemical and material, therefore everything in man is chemical and material, and because man is pre-moved, therefore he is also pre-determined, is neither good logic nor good science. "As if we were villains of necessity, Knaves, thieves and liars by spherical predominance; drunkards, liars and thieves by an enforced obedience of planetary influence!" Winston Churchill gave even shorter shrift to the spiritless deterministic psychiatrists, in vol. IV of *The Second World War*. The opinion of the regimental sergeant-major, about the recruit "determined" to keep out of step, was unprintable—but justified.

Dr. Madison says that "the existence of 'good' and 'bad'" are "products of the human mind". So the apple which I threw out was not really bad, but I was bad-minded. And "the facts of morality" are merely "products of the human mind". Which means that respecting my neighbour's property is not good in itself, nor is thieving bad in itself. But only as my mind, or the mind of a dictator, makes them!

However, there is hope for Dr. Maddison yet. He introduces "accountability", which is not accountable except from free will. And he contradicts his own doctrine by informing us that "civilised man naturally assumes responsibility for the effects of his action on others".

Sydney. V. J. KINSELLA.

POSTCOITAL EXAMINATION OF SEMEN

SIR,—I was deeply perturbed by Mr. Dunn's letter in your issue of Nov. 28. The investigation and treatment of subfertility, especially in the male, have made considerable advances in the past ten years, and if we accept Mr. Dunn's arguments and methods we shall deprive our patients of the help they can expect from us.

First of all, I should like to challenge the assumption that subfertile men cannot be improved. Since the time when we began to realise the importance of testicular temperature regulation, and the effects of its disturbances upon spermatogenesis, it has become a commonplace to see subfertile men recover. A letter such as this is not the place for extensive explanations and references, but I shall be glad to supply the latter to anyone interested. For the present I will only say that I have not met anyone with *personal* experience of these methods who maintains Mr. Dunn's and his authorities' traditional pessimistic outlook.

If it is true that subfertile men may be improved, then obviously a precise and consistent method of semen examination is essential in assessing the patient's original state and progress. This, of course, requires seminal specimens produced by masturbation or coitus interruptus, and there is no adequate alternative. The method of "postcoital urethral drainage" may not have been described in the literature, but I have met with patients investigated in this way repeatedly. One such case was sent to me with an inquiry whether his apparent sterility was beyond repair; a proper semen test showed him a highly fertile man, and his wife conceived promptly after correcting a minor fault on her side. Another man investigated in this way had prolonged courses of hormones and vitamins intended to cure his "oligozoospermia". Finally he was given a hopeless prognosis, but a proper semen test also showed perfectly normal findings. The postejaculatory urethral residue is in no way representative of a man's fertility and any verdict based upon it must be regarded as guesswork.

The postcoital test has been in constant use for many years and I think one may regard it as a sine-qua-non in the investigation of an infertile couple. After all, the first require

1. Dodds, E. C. *Proc. R. Soc. Med.* 1950, **43**, 343.

ment for fertilisation is a dense and active sperm population in the cervix, and without this further gynæcological investigation may be a waste of time. But despite its very great value, this test has its limitations. Unless we are quite clear as to what it can and cannot tell us even a perfectly conducted postcoital examination may mislead us disastrously. Mr. Dunn's statement that failure to find spermatozoa in two postcoital tests suggests an azoospermic husband is truly alarming! I see amongst my patients quite regularly couples who produce persistently "blank" postcoital results, despite good semen, œstrogenic mucus, and apparently perfect sex function: these are cases of a purely "mechanical" failure of insemination, and there are quite a number of reasons why this may happen. Some uterine displacements may turn the cervix into one of the fornices, shielding it from the ejaculate; the couple may use a coital position making for poor penetration; a parous vagina may be so lax that the ejaculation takes place into a pocket of loose mucosa and sperms never reach the cervix; the man may have a hypospadias; and so on. A complete list would overburden this letter, but anyone familiar with the postcoital test will be aware of the problem. Incidentally, the correction of these faults usually proves very simple, once the diagnosis is established.

I must also raise some criticism of technical details of the postcoital test as described by Mr. Dunn.

Firstly, to remove only a drop of cervical mucus with artery forceps may produce very misleading findings. I usually aspirate the whole contents of the cervical canal, and time and again I find some portions of the mucus poorly invaded, or even "blank", when other portions may be teeming with active spermatozoa. Therefore poor findings in only one drop of the mucus may be of no significance.

Secondly, for the same reason, it is patently impossible to estimate the husband's sperm density from even a complete aspirate of the postcoital mucus since we should not know which of the variedly populated fractions is representative.

Thirdly, it is useless to attempt an estimate of the husband's sperm morphology from even a stained postcoital preparation. Only the best spermatozoa invade the mucus since most of the abnormal forms are either immotile or sluggish. In the past, when I used to stain my postcoital specimens as a routine I frequently found in them no more than 3–4% of abnormal spermatozoa, even when the direct semen test might show up to 40–50% of morphological abnormalities. I believe this is generally recognised by workers who use this method.

Lastly, it is surprising to see the statement that in the postcoital test "occasionally motile spermatozoa are seen after sixteen hours". Many of us have seen excellent postcoital results 2–3 days after intercourse, and a few live spermatozoa even after 6 days. Most of my own routine tests are done 10–16 hours after coitus, and personally I am inclined to regard a postcoital test after less than 2 hours as of doubtful value. For what we want to learn from this test is whether good numbers of healthy spermatozoa survive in the cervix after being exposed to the hazards they must encounter. And after 2 hours or less many spermatozoa may still be alive which will never reach the cervical canal, or survive in it if they do.

One might scrutinise the reasons for introducing these indirect and roundabout methods instead of the well-tried direct semen test. Mr. Dunn mentions moral standards and overlooked sensibilities. The former, I should say, would apply only to certain religious denominations. To many men the act of masturbation or coitus interruptus, in a most worthy cause, is not more a moral issue than the gynæcologist's examination is to their wives. As to sensibilities, one might ask whether a man who feels deeply would expose his wife to embarrassing and sometimes painful investigations before eliminating the approximately 40% chance that he himself carries the main infertility factor. Among my own series of over 12,000 husbands the incidence of complete azoospermia is little short of 10%, and that of grossly impaired semen very much higher. It is obvious therefore that failure to assess the male factor accurately would condemn many women to a great deal of unnecessary investigation, discomfort, and eventual frustration. My personal impression is that usually a man's reluctance is based upon fear of being found at fault. This, I think, applies equally to women, yet we do not hesitate to examine them. And just as we can reassure a frightened woman by explaining the need for precise diagnosis, a man will be capable of overcoming his misgivings if we appeal to his reason and his sense of fairness.

London, W.1. H. A. DAVIDSON.

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—There appears to be some misdirection of emphasis in Dr. Nour-Eldin's letters (Nov. 21 and Dec. 12) on the thrombotest devised by Professor Owren.[1] This new method is not designed to detect Christmas disease but to control anticoagulant therapy during which Christmas factor in addition to prothrombin and factor VII are depressed. Even if the method is shown to be only a little more sensitive than existing *practical* ones the contribution of Professor Owren cannot be ignored.

We have been fortunate in having had several months' experience with thrombotest. The essential reagent is sent out in lyophilised form easily reconstituted in a few minutes and the test is very simple to perform. Our final assessment is nearly ready for publication.

In two cases of Christmas disease tested by us with thrombotest the clotting-times were about 10 seconds longer than normal. Professor Owren, in a personal communication, has pointed out that when the test is carried out with plasma from a case of Christmas disease (concentration of Christmas factor below 1% of normal and all the other factors at 100% of normal) and then with plasma from a normal subject (concentration of all the factors at 100% of normal) the difference in clotting-times was only 6–8 seconds. However, when the extrinsic clotting system is depressed during anticoagulant therapy the sensitivity to depressions in Christmas factor increases, using dilute thromboplastin reagents.[2]

The thrombotest reagent appears worthy of careful clinical trial and may well prove to have a place in the routine control of anticoagulant therapy. It is apparently being used extensively in Scandinavia.

Anticoagulant Therapy Service,
Department of Clinical Pathology,
Manchester Royal Infirmary. H. LEMPERT
L. POLLER.

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—A number of investigations essential to the diagnosis or management of disease are demanded so rarely or are technically so inconvenient that they are not everywhere readily available. They are often done as a courtesy by interested research-workers, who naturally may not undertake them always or promptly.

Now that the Public Health Laboratory Service is being remoulded, the National Health Service might well establish a central laboratory able to estimate routinely follicle-stimulating hormone, urinary catecholamines, protein-bound iodine, and transaminase, to name only a few of the tests occasionally required by the general physician. It would play a role in biochemical and endocrinological diagnosis as important as that of the bacteriological reference laboratories in their sphere.

Oxford. T. H. HUGHES-DAVIES.

1. Owren, P. A. *Lancet*, 1959, ii, 754.
2. Waaler, B. A. *Scand. J. clin. lab. Invest.* 1957, **9**, 322.

Obituary

HUGH DONOVAN

M.B. Birm., F.R.C.S., F.R.C.S.E.

Mr. Hugh Donovan, senior urologist to the United Birmingham Hospitals, died on Dec. 6.

Born in 1897, the son of Lieut.-Colonel R. T. Donovan, R.A.M.C., he was one of a family of doctors well known in the Midlands. He was educated in Birmingham at King Edward's School and the university. During the 1914-18 war he served in destroyers as a surgeon-probationer, and he did not qualify until 1919. He was one of Prof. Seymour Barling's notable band of house-surgeons, but he did not immediately turn to surgery, for he joined the Indian Medical Service for a brief spell. But once he had chosen surgery as his specialty his chief interest was always urology, and he studied this subject in London, where he was for a time a clinical assistant at St. Peter's Hospital, before he was appointed assistant surgeon to the Queen's Hospital in Birmingham. He remained a general surgeon with this special interest until shortly after the late war, when the death of his senior colleague, B. J. Ward, left him with more and more urological work. Finally Donovan gave up general surgery entirely. This change enabled him during the last decade to lay the foundation of a urological department, and his success was lately recognised by an invitation to become president of the British Association of Urological Surgeons in 1960, an invitation which he had to refuse because of ill health.

B. N. B. writes:

"It is my misfortune to have known Hugh Donovan only during the last twelve years, for throughout these years he appeared a lonely man seeking solace in work after the early death of his wife, to whom he had been devoted. But this is not to say that he was unapproachable; indeed to be *à deux* with him was to be sure of amusement and gentle understanding. Despite occasional moments of contention, moments which revealed the degree of his usual self-control, gentleness pervaded his surgical life and his everyday affairs—gentleness mixed with charm and whimsy, both reminders that his Irish ancestry was stronger than his Midland upbringing. Courage he had in full measure; he did not hesitate to transect the vena cava in order to transpose a ureter where lesser men would have quailed, done the reverse, and risked a ureteral stricture later. He was industriousness personified, even to a fault, since it never occurred to him that his own unceasing labours necessarily involved others and might bring them to exhaustion; not that his junior staff ever complained, since his approach to any subject, conventional or otherwise, was from such an unusual slant that it would be certain to stimulate or amuse—often both. Over and above there was the transparent honesty and integrity of a man tested beyond personal ambition."

DOROTHEA CLARA NASMYTH

M.A. Dubl., M.D. Lond.

Dr. Dorothy Nasmyth, who died on Dec. 12, was something of a pioneer. She was the first woman to read physiology at Oxford (and one of the few who have ever taken a first in this subject) and she was the first woman general practitioner in Oxford. She qualified in 1906 and during the 1914–18 war worked in Serbia during the typhus epidemic.

A. M. writes:

"Dorothy Nasmyth's small stature, quiet voice, and slow speech hid an outstanding intellect, almost uncanny powers of perception and judgment, and a great devotion to medicine and to people. But she was not ambitious. She rejected the chance of an academic career because she loved general practice. Her clinical judgment was remarkable and to the end of her life she often made diagnoses which seemed to be both unlikely and extraordinary, but which time or investigation proved to be correct. She read widely in many branches of medicine and always made a point of learning what she could from any specialists, younger doctors, or medical students who came her way. Her humble approach often gave them the impression that she was old and out of date, but her immediate understanding and her perspicacious comments soon revealed her wide knowledge of even the most modern developments. Until her final illness she continued to attend lectures and clinical meetings, often driving many miles to do so.

"She had many interests outside her work. Perhaps the chief of these, apart from devotion to her husband and family, was a love of animals. I first met her when I was ten, through the riding-school that she ran with her son and daughter. The friendship, despite an age difference of some forty-five years, continued to develop until her death, for she had the ability to cross the barrier between generations. She could talk as one individual to another with people of any age. She seemed to retain in maturity and age the essence of childhood and youth that most people lose in passing."

DAVID ARTHUR KETCHEN CASSELLS

M.D. St. And., M.R.C.P.E.

Dr. D. A. K. Cassells, formerly chief medical officer to the alkali division of Imperial Chemical Industries, died on Dec. 16 at Northwich.

He was born in Fife in 1896, the son of a Scottish dominie. After serving in the 1914–18 war as a combatant, he qualified from St. Andrews University in 1923. He held house-appointments at Dundee Royal Infirmary and then went into general practice in Herefordshire. In 1938 he took the M.D. at St. Andrews with honours and left his practice for further study at the Postgraduate Medical School of London, taking the M.R.C.P.E. in 1939.

In 1940 he became medical officer to a factory where for the first time in this country tetraethyl lead was manufactured. The process was full of little-known hazards, but because of his continuous vigilance there was no case of intoxication in the factory. Cases, however, did occur elsewhere from time to time, and he was often called in to advise. In 1946 with Sir Charles Dodds he published a classic account of tetraethyl-lead intoxication, including 25 case-histories. During the late war he was appointed consulting physician to the Victoria Infirmary, Northwich, where he helped to set up a small panel of blood-donors which, until blood-banks came into being, was of great use. After the war he became the first full-time chief medical officer of the alkali division of I.C.I. He retired in 1958. Outside his work he found relaxation in bridge and fishing. He leaves a widow.

Diary of the Week

JAN. 3 TO 9

Tuesday, 5th

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. Joseph Minton: Ocular Manifestations in Clinical Neurology.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Prof. David Whitteridge: The Calcarine Cortex and Cerebral Organisation.

Wednesday, 6th

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5 P.M. Dr. Ellis Dresner (Harvard): Latex Fixation Reaction.

Thursday, 7th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Neurology*. Dr. J. B. Cook, Mr. Thomas Moore, Mr. D. Innes Williams: The Paralysed Bladder.

Friday, 8th

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Anæsthetics*. Dr. A. R. Hunter, Dr. J. M. Inglis: Value of Controlled Respiration in Neurosurgery.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. C. Gill-Carey: Otitis Media.

Notes and News

THE PREP SCHOOL

PREPARATORY schools are facing a difficult future; for in the next few years, as State schools and independent schools move closer together, more and more boys are likely to enter or leave preparatory schools at the age of 11. A short report [1] on them which has lately appeared is of exceptional interest, because it reconsiders the aims of teaching without much regard to the requirements of the public schools. At present the universities call the tune to the public schools, which in turn impose a pattern upon the preparatory schools. With greater mobility within the educational system this stranglehold will relax; and even now there are, it seems, more boys in preparatory schools than the public schools can accommodate.

The report is unusually imaginative. It argues that Latin should be taught only to those likely to be academically capable of benefiting from it, and it recommends a later start in this subject. The section devoted to the early teaching of science is especially good. Regarding such teaching as a means of "stimulating interest in natural things and of supplementing a boy's inherent interest in how things work", it goes on to outline a syllabus actually in use which appears to be unexceptionable. The need for a drive for greater literacy and fuller attention to cultural interests is emphasised. There is an admirable section on the opportunities inherent in the conception of physical education.

Parents and those interested in the generation now growing up will find this report stimulating. It is hard to avoid a sense of frustration when one realises how much could be done if there were only the money. No reference is made to the lamentable shortage of good teachers in preparatory schools today. The position is getting worse as the older ones go. Unless and until the conditions and pay attract the right men, there is small hope of these brave recommendations being fulfilled.

CLEANSING AND STERILISATION OF HOSPITAL BLANKETS

EFFORTS are being made in many hospitals to improve the hygiene of bedding and to provide each patient with freshly laundered and disinfected blankets. This is certainly desirable on æsthetic grounds, and there are apparent though unproven bacteriological advantages. But hospital authorities wishing to consider these matters must search widely for the available facts and opinions. The King Edward's Hospital Fund for London has now done this for them, and its interim report [2] contains extracts from many published papers and from replies to a questionary sent out by the Fund's division of hospital facilities. The subjects discussed include the role of unsterilised blankets in hospital cross-infection, the problems of washing and sterilising them, and the different types of blanket that are now to be had, their cost, and their acceptability to patients and nurses. On very few of these problems can a clear answer yet be given, and it is perhaps a pity that this interesting summary has been published before some of the current large-scale investigations are complete. Nevertheless, it brings together a set of references which will be useful to those who are planning trials of their own.

HOSPITALS YEAR BOOK

THE new edition of this useful and hardy annual [3] has appeared punctually and will be at hand during 1960 to offer reliable information. Besides the hospital directory there are sections giving particulars of blood-transfusion services, Government departments, statutory bodies and organisations, local health authorities, executive councils, Whitley councils, and hospital contributory and provident schemes. A substantial reference section includes indexes to statutory instruments and official circulars, legal notes, and summaries of reports; and a short bibliography of recent publications about hospital topics ranges from "accounting and finance" to "staffing". Mr. J. F. Milne, the editor, in his survey of the past year soberly discusses the problems which dog all progress. He welcomes the new Mental Health Act but warns that its effect may be hindered by lack of money and staff. He welcomes work study as a necessary tool for a modern service, but points to the danger that "time and effort devoted to work study will not be matched by commensurate time and effort in applying its results".

1. Foundations: report of a committee appointed by the council of the Incorporated Association of Preparatory Schools. Ipswich: W. S. Cowell. 1959. Pp. 47. Copies may be had from R. A. Harrison, Snape Hill, near Saxmundham, Suffolk, for 2s. (post free).
2. An Interim Report on the Cleansing and Sterilising of Blankets. King Edward's Hospital Fund for London, 34, King Street, London, E.C.2. Pp. 59. 2s. post free.
3. Hospitals Year Book 1960. London: Institute of Hospital Administrators (75, Portland Place, W.1). 1959. Pp. 1166. 59s. 6d.

University of Cambridge

On Dec. 12 the degree of M.CHIR. was conferred on P. P. Philip (by proxy).

University of Durham

On Dec. 19 the degrees of M.B., B.S. were conferred on the following:

Bandele Akinola Aboyade, Lilian F. C. Beattie, Kenneth Beveridge, Kenneth Bolam, T. M. Bolam, Moira M. A. Browne, W. K. Deegan, J. D. Etherington, J. G. Goundry, P. J. K. Maskery, G. W. Odling-Smee, Christine M. Peacock, F. A. Rafique, Susan J. Richardson; Mashood Babatunde Odemuyiwa (in absentia).

University of Leeds

At recent examinations the following were successful:

M.D.—John Gibson, T. K. Marshall, Ronald Spink.

M.B., Ch.B.—Helen M. Hoyle, J. M. S. Pearce, J. H. Wetherill (second-class honours); Jill E. Awcock, J. A. C. Bailey, Walter Barnes, Ann G. Benson, R. E. Blagg, A. G. Bond, Ian Cliffe, J. A. Dacre, Irene M. Dunderdale, Shirley M. Ewart, T. R. Forrest, Kenneth Fox, J. M. France, Margaret Hallas, Dharmchand Heeralall, Jennifer A. Homeshaw, R. V. Howarth, Derek Hoyle, Florence S. Hutchinson, Hamid Ikram, K. J. Kedwards, G. P. Kirkland, D. H. Mellor, Kenneth Oldroyd, B. A. Pell, Raymond Plowman, Elizabeth Rowe, Eddys E. Sherwood-Cundall, Kenneth Thornber, R. A. N. Welham, Elizabeth A. Wilford.

University of Liverpool

On Dec. 18 the following degrees and diplomas were conferred:

M.D.—Constance M. Davis, D. A. P. Evans, J. E. Riding, J. G. Warbrick.

Ch.M.—*Ranjit Basu, *Roger Brearley, John Humphreys, *P. K. Tamaskar.

M.Ch.Orth.—A. C. Da Roza (gold medal); J. A. Adams, K. V. Chaubal, A. W. B. Heywood, D. C. MacPhail, B. T. O'Connor, M. Y. Rai, M. L. Rajakaruna, *B. F. Regan, L. N. Vora.

M.B., Ch.B.—Geoffrey Balderstone, K. R. Ball, T. D. Birtles, J. A. Q. Blukoo-Allotey, Judith M. Burgess, Kenneth Cartwright, Essillt Evans, R. G. V. Hughes, B. H. E. James, J. H. Lloyd, G. W. McKenna, C. J. Merry, Patricia A. Moore, Ronald Pactor.

D.M.R.D.—P. Daranond, H. F. Davies, C. D. Krasner.

D.M.R.T.—Varunee Amatyakul.

D.T.M. & H.—D. R. Bell, G. N. Bhadresa, S. M. Bieber, R. M. Briggs, J. R. Cope, A. A. Darkwa, D. S. Gilchrist, D. R. W. Haddock, R. Harris, R. B. Hawes, M. M. Husainee, T. D. Jeyachandran, W. L. Johnson, E. D. Mahajan, G. D. E. Morris, M. A. Newland, W. I. B. Onuigbo, C. R. Rao, V. R. Rao, K. B. H. Reddy, J. H. Rouch, J. T. Sorley, L. F. Tinckler, L. Tsere, Sutee Ujjin, J. T. Weir, D. G. Young.

* In absentia.

University of Manchester

At recent examinations the following were successful:

M.B., Ch.B.—G. A. Cumming, Shirley Currie, T. C. Davies, P. L. S. Dixon, D. L. Easty, Valerie K. Frazer, F. A. Hindley, F. R. Hirst, C. E. Horsfall, W. R. Hutton, M. J. Imrie, A. W. Jackson, J. H. Jones, Frank Kemble, N. P. Mallick, Shirley A. Maxwell, Doreen Millns, Rosemary G. Mitchell, K. J. Noblett, Doris E. Probert, Diana H. Seddon, Shirley E. Stanworth, J. R. Thelwell, J. B. Thomson, Margaret Ward, Sylvia A. Wood.

University of Sheffield

Dr. John Knowelden has been appointed to the chair of preventive medicine and public health.

He was educated in London at King's College and St. George's Hospital. After qualifying in 1942, he served as a surgeon lieutenant in the R.N.V.R. till 1946. After demobilisation, with a Rockefeller fellowship in preventive medicine he spent a year at the Johns Hopkins School of Hygiene and Public Health, Baltimore. In 1949 he was appointed to his present post of lecturer in the department of medical statistics and epidemiology at the London School of Hygiene and Tropical Medicine. He is a member of the Medical Research Council statistical research unit, and he was secretary of the M.R.C. poliomyelitis vaccines committee which conducted the 1956 field trial of British poliomyelitis vaccine. Dr. Knowelden is a joint editor of the *British Journal of Preventive Medicine*.

University of Bristol

At recent examinations for M.B., CH.B. the following were successful:

R. I. A. A. Aubee, J. A. G. Benson, G. C. Duff, H. W. Haskins, D. R. M. Heighton, J. P. A. Hill, R. C. Hodge, G. W. E. Lockett, Madeline D. Mayne, D. T. H. Randell, Dorothy M. I. Sibbald, D. J. Stayte, Madueke Ugwunze, Ranjit Jayakar Undugodage.

University of Edinburgh

On Dec. 18 the following degrees and diplomas were conferred:

M.D.—R. R. Gillies, *C. G. I. Gordon, J. C. Gould, R. S. McNeill, H. W. Simpson (commended for thesis); Morag S. Macdonald.
Ph.D. (in the faculty of medicine).—A. W. Williams.
M.B., Ch.B.—J. W. S. Angus, J. A. Birtchnell, J. B. McG. Fleming, J. D. Gilleghan, Peter Gordon, D. J. Harrison, J. M. Henderson, R. G. McGown, C. J. McKeown, J. A. L. Mayhew, R. G. Moses, J. E. M. Robertson, R. T. A. Ross, W. G. Russell, Prasert Sukhum, W. R. Sullivan, R. N. T. Thin, T. G. S. Wilson.
D.P.H.—Agnes E. Whitter.
D.M.R.D.—A. A. H. Brown, G. M. Fraser, A. F. MacDonald, I. R. Pyle.
D.M.R.T.—James Frame, J. F. Pringle, H. G. Whiston.
* In absentia.

Queen's University of Belfast

Dr. W. E. Glover has been appointed supernumerary lecturer in physiology.

Royal College of Surgeons of Edinburgh

At a meeting of the college on Dec. 18, with Prof. John Bruce, the president, in the chair, A. H. Jacobs, P.R.F.P.S.G., V. C. Rambo, F.A.C.S., and J. D. Wade, F.R.C.S., were admitted fellows without examination.

The following were admitted to the fellowship:

J. B. Anchen, B. J. Bowden, B. C. Bracken, Manindra Nath Brahma, D. Pui-Chee Chan, Raghunath Deshika Char, G. D. Chisholm, E. Poh Hwye Chu, E. C. Cowan, A. C. B. Dean, Lakshman Chandra Dutta, Anup Mangesh Gokarn, P. A. Goodwin, C. E. Graham, E. C. G. Lee, Brijlal-Chananram Gupta, S. D. Holloway, Mominul Huq, A. R. Isaac, G. R. James, Vasant Venkatrao Kayarkar, J. A. Kennedy, I. F. Kerr, K. G. Kling, Izak Labuschagne, W. M. L. Laubscher, H. I. Leigh, P. J. Lethlean, J. H. Lowry, Abdel Wahab Reda Mabrouk, J. G. Mathie, Brian Measday, Mookkassan-airveettil Pullare Achutha Menon, K. K. Merten, W. G. Millar, J. C. Milliken, Shaikh Mohammad Monif, John Morgan, Jack Norman-Smith, T. G. O'Donovan, Thotathil Achuthan Paraman, Ponnampalam Paramaswaami, P. R. Payne, R. S. Phillips, Madhav Mohan Rao, W. H. Reid, Victor Romanowski, Subramanian Shanmugam, Inder Dev Sood, R. W. Springhall, James Tevendale, R. N. Tinning, M. A. Turner, Madho Prashad Vaidya, Mohomad Waliuddin, A. B. Young.

Dr. Stephen Plumpton has been elected and Dr. D. C. Hall admitted to the fellowship in dental surgery.

Society of Apothecaries of London

The following diplomas have been granted:

L.M.S.S.A.—R. J. Annison, R. Cook, G. A. Lee. G. H. E. Woodbine, Y. Y. Liu, C. P. Juniper, G. Davies, H. A. Gordon, J. E. Igwe, P. R. S. Johnson, Z. F. M. Newton-Nowinski, R. Tiru-Chelvam.
M.M.S.A.—N. K. Allahbadia, M. H. Kyi, U. N. Pathak.
D.I.H.—G. J. Clarke, R. H. P. Fernandez, N. Y. Prakash, A. R. Prasad, S. Prasad, M. P. Y. Scott, R. R. L. Wild.

Royal Society of Medicine

William Gibson research scholarship (£200).—Applications for this scholarship are invited from British women doctors. Further particulars may be had from the secretary of the society, 1, Wimpole Street, London, W.1. The closing date for entries is May 1.

International Congress of Clinical Pathology

This conference is to be held in Madrid from June 13 to 17. There is to be a section of forensic pathology with discussions on unknown causes of death with minimum visible lesions, chemical investigations in cadaver blood, and accidents in sanguineous transfusion. Those who wish to contribute papers should write to Dr. F. E. Camps, department of forensic medicine, London Hospital Medical College, Whitechapel, E.1, before Jan. 1.

Applications for an Eli Lilly medical research fellowship ($300 a month for twelve months and travelling expenses) are invited from doctors registered in South Africa who wish to undertake research in the United States. Further details can be obtained from Dr. H. A. Shapiro, P.O. Box 1010, Johannesburg. The closing date for applications is April 30.

Twelve postgraduate travelling scholarships of £350 each are to be awarded by the British Commonwealth Nurses War Memorial Fund to nurses and midwives for study during 1960–61. Further particulars may be had from the secretary of the Fund, Dorset House, Stamford Street, London, S.E.1.

Central Middlesex Hospital research prizes (each of £50) have been awarded to Mr. K. Lloyd-Williams and Dr. W. H. Summerskill.

The British Dietetic Association (251, Brompton Road, London, S.W.3) is offering a grant of £250 from the Rose Simmonds Fund for study or research in dietetics.

A meeting of the Osler Club of London will be held on Thursday, Jan. 14, at 8.15 P.M., at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1. Prof. W. E. Kershaw and Prof. P. C. C. Garnham will speak on the history of parasitology.

Semi-permanent exhibitions will be held during the winter term at the Institute of Dermatology, Lisle Street, London, W.C.2. The first, from Jan. 4 to 27, will be by Dr. William Frain-Bell on drug eruptions.

The Ministry of Power has published its digest of statistics of pneumoconiosis in the mining and quarrying industries for 1958. Copies may be had from H.M. Stationery Office (3*s*. 6*d*.).

A revised British Standard for rubber-proofed bed sheeting for hospital use has been published (B.S. 2508: 1959). Copies (price 4*s*.) may be obtained from the British Standards Institution, Sales Branch, 2, Park Street, London, W.1.

Appointments

DE SOUZA, W. D., M.B. Bombay: orthopædic registrar, Peterborough group of hospitals.

HOGARTH, T. B., M.B. Leeds, F.R.C.S.E.: part-time consultant in otolaryngology, Scarborough, Bridlington, and Whitby area hospitals.

KERR, W. F., M.B. W'srand, F.R.C.S.E.: senior registrar in thoracic surgery, Papworth Hospital, Cambridge.

LAGOWSKI, ANATOL, M.D. Lwow, D.A.: assistant anæsthetist (S.H.M.O.), Scarborough, Bridlington, Malton, and Whitby group of hospitals.

LEONARD, B. J., M.D. Manc.: consultant pathologist, Derby group of hospitals.

PALEY, R. G., M.D., PH.D. Leeds, M.R.C.P.E.: consultant physician (with special interest in geriatrics), South East Northumberland, Wansbeck, Alnwick and Rathbury, and Berwick upon Tweed groups of hospitals.

SOMNER, A. R., M.D. Edin., M.R.C.P.E.: consultant chest physician, South East Northumberland and Newcastle upon Tyne groups of hospitals.

The Hospital for Sick Children, Great Ormond Street, London:

BRUCE, A. W., M.B. Aberd., F.R.C.S.E.: surgical outpatient assistant.
EVANS, RACHEL G., M.B. Lond.: house-physician.
INALL, J. A., M.B. Sydney, D.C.H.: house-physician.
SIMPKISS, M. J., M.B. Birm., M.R.C.P.: resident assistant physician.
TALWALKER, V. C., M.B. Bombay: house-surgeon.

South-Eastern Regional Hospital Board, Scotland:

CONACHER, W. D. H., M.B. Glasg., M.R.C.P.E.: consultant physician, West Lothian group hospitals.
HORTON, JEAN M., M.B. Lond., F.F.A.R.C.S., D.A.: consultant anæsthetist, department of surgical neurology, Western General Hospital, Edinburgh, and Edinburgh Royal Infirmary.
LAIDLAW, JOHN, M.B. Edin., M.R.C.P.E.: clinical neurophysiologist (S.H.M.O.), department of surgical neurology, Edinburgh.
PETRIE, P. W. R., O.B.E., M.B. Edin., D.T.M. & H., D.P.H.: assistant S.A.M.O. to the Board.
SMITH, A. W. M., M.B. Edin., M.R.C.P.E.: consultant physician, Fife area hospitals.

Welsh Regional Hospital Board:

DAVIES, T. S., M.R.C.S., D.P.M.: consultant in mental deficiency and medical superintendent, Llanfrechfa Grange, near Cwnbran.
LEITCH, G. B., M.B. Dubl., F.R.C.S.E., D.L.O.: consultant E.N.T. surgeon based at Royal Gwent Hospital, Newport.
PACKER, R. E., M.B., B.SC. Wales, D.O.M.S.: consultant ophthalmologist, Glantawe H.M.C. area.
THOMAS, T. J., M.R.C.S., D.M.R.D.: consultant radiologist, Merthyr and Aberdare H.M.C.

Colonial Appointments:

BLENKINSOPP, E. M., M.R.C.S.: district M.O., St. Vincent.
DAWSON, I. E., M.B. Glasg.: medical superintendent, Zanzibar.
FISHER, P. W., M.B. Cantab.: M.O., South Pacific health service.
GOULDING, M. D., M.B. Madras, D.T.M. & H.: registrar, health department, Trinidad.
GUY, W. D., M.B. Glasg.: M.O., Northern Region, Nigeria.
HURLEY, D. W. H., M.B. N.U.I., F.R.C.S.: surgeon specialist, Zanzibar.
LOCKHART, J. D. F., M.B. Dubl.: M.O., Kenya.
MUSSON, FRANCES A., M.R.C.S.: M.O., Northern Region, Nigeria.
TRUELSON, KAREN E. T., M.D. Copenhagen, M.P.H.: M.O.H., Northern Region, Nigeria.

Births, Marriages, Deaths

DEATHS

TURNBULL.—On Dec. 23, after a short illness, Dr. Peter Mortimer Turnbull, M.C., M.B., of 63, Woodbourne Avenue, Streatham, S.W.16, late medical superintendent of Tooting Bec Hospital, aged 80.

A PLACE FOR HISTAMINE IN NORMAL PHYSIOLOGY *

GEORG KAHLSON
M.D. Munich and Lund, Hon. M.D. Oslo
PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF LUND, SWEDEN

UNTIL very recently studies on histamine were mainly concerned with its distribution, liberation, origin, and mode of binding. This " static " approach to the problem, imposed by limitations in available methods, has led to the present impasse in the interpretation of the physiological significance of histamine. A more dynamic approach would place less emphasis on the content than on the rate of formation, the rapidity of turnover, or the rate of " usage " of the amine. In Lund our interest was first turned in this direction by the observation that cats could be starved to the extreme without any concomitant change in the content and distribution of histamine (Haeger and Kahlson 1952). Even removal of the pituitary gland or adrenals did not cause such changes (Haeger, Jacobsohn, and Kahlson 1952). Complete inhibition of the histamine-destroying enzyme histaminase did not influence the tissue content of histamine (Kahlson, Rosengren, and Westling 1958a). We further found evidence of a kind of regulatory mechanism designed to keep constant the tissue level of histamine in the gastrointestinal tract (Haeger, Kahlson, and Westling 1953). All this suggested that the actual tissue content of histamine is a poor indicator of changes in the metabolism of the amine. Consequently we decided to study the spontaneous liberation and rate of formation of histamine under various physiological conditions.

The Origin of Histamine

No methods are available for the accurate estimation of the small changes in the histamine level of blood or plasma which might possibly occur in physiological conditions.

Gaddum (1951) and his colleagues suggested that estimation of histamine in the urine is more likely to give information about the release of histamine in the body than investigations on blood. But this approach is limited by the fact that the food commonly eaten by man and laboratory animals contains substantial amounts of histamine, part of which is excreted in the urine. Further, with such a diet intestinal bacteria decarboxylate histidine to histamine, so adding more exogenous histamine. Large amounts of urinary histamine derived from exogenous sources are likely to conceal increases in urinary histamine derived from increased production or spontaneous release of endogenous histamine.

The complications due to exogenous histamine can be overcome. With two colleagues (Gustafsson, Kahlson, and Rosengren 1957) I investigated the distribution and urinary excretion in germ-free-reared rats fed on a special histamine-free diet, and compared these results with those from ordinary rats fed on the same diet. The distribution and urinary excretion of histamine were largely identical in the two groups of rats, indicating that, when the histamine-free diet is given, the histamine excreted and contained in the tissues is endogenous in origin both in germ-free and normal animals. In the male rat urinary histamine is mainly in the conjugated form. In the female rat, fortunately, the urinary histamine is almost exclusively in the free, biologically active form, which allows assay directly on the isolated ileum of the guineapig. The urinary excretion in what I shall call our " standard rat " thus provides a useful baseline for our studies, and I shall show by further experiments that in this rat the urinary excretion of histamine runs parallel with the rate of formation.

Inhibition of Histamine Formation in Vivo

Until recently no means were known for measuring in vivo the rate of histamine formation. Studies of the urinary histamine in the female rat, measured by the isotopic methods devised by Schayer (1959) have so far proved most useful. (Indeed Schayer's work has contributed decisively to a new era in histamine research.) The isotopic method depends principally on the injection of ^{14}C-histidine and measurement of ^{14}C-histamine and its metabolites excreted in the urine. In the female rat diamine oxidase (histaminase) is the main histamine-destroying enzyme, and aminoguanidine is its specific inhibitor. Under the influence of aminoguanidine a larger proportion of the histamine formed will be excreted in the urine.

Histidine decarboxylase, the enzyme which converts histidine to histamine, can be inhibited in vitro by semicarbazide, but this inhibition is neither very strong nor specific. Miss Rosengren and I have injected our standard rat with semicarbazide in gradually increasing doses, and studied the urinary histamine output over periods of days or weeks. For the first day or two the urinary histamine is lowered, and then, despite the sustained influence of the inhibitor, the original histamine output is restored. When the injections are discontinued, however, the urinary histamine rises far above normal values, suggesting that the enzyme inhibition is overridden by the simultaneous formation of new molecules of histidine decarboxylase. We were able to overcome this " escape " from the influence of the inhibitor by feeding the standard rat on a diet deficient in pyridoxine, a coenzyme of histidine decarboxylase. On this diet semicarbazide in gradually increasing doses reduces the histamine formation to as little as 20% of normal (fig. 1); the animal appeared fairly fit as regards appetite, exercise, and maintenance of body-weight. When semicarbazide is discontinued the striking increase in urinary histamine reflects the overshoot in histamine formation. The histamine content of the skin of the back, abdomen, and ears was examined before and at the time of greatest inhibition of histamine formation. The two sets of figures did not differ, and they show the lack of correlation between content and rate of formation in the skin. This inconsistency can be accounted for by assuming that all binding sites are occupied and that the histamine molecules are held there even when histamine is formed at a very low rate. If this is true, then even a strong histamine inhibitor is unlikely to counteract the adverse effects of histamine liberated in anaphylaxis or allergy. Measures aimed at hindering or tightening the coupling of histamine to the binding sites seems, a priori, more promising as a remedial approach. Cortisone seems to hinder the coupling of histamine to the binding sites (Schayer 1956).

* A lecture (abbreviated) delivered in the department of pharmacology of Oxford University, in May, 1959, and at the University of Liverpool, in November, 1959.